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(54) 21-SUBSTITUTED STEROID COMPOUND

IN STELLUNG 21 SUBSTITUIERTE STEROIDE

COMPOSE STEROIDE SUBSTITUE EN POSITION 21

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Description

Field of the Invention

[0001] This invention relates to novel steroidal comopunds substituted at position-21 with simple sugars or acylated derivatives of said simple sugars.

Background of the Invention

[0002] Development of sugar-steroid compounds which have no steroidal activities themselves, but can be converted to the active forms by glucosidases which increase at the inflammatory site of rheumatism or the like have been reported by the research group of Merck & Co. [J. Am. Chem. Soc. (1964), 86, 3903-4, FR3627 (1965) and GB1015396 (1965)]. Specifically, GB-A-1015396 relates to 21-glucuronide derivatives of steroids of the pregnane series and discloses in Experiment No. 10 on page 7 the intermediate butyl [(9 α-fluoro-6,16α-dimethyl-11 β, 17 α-dihydroxy-1,4,6-pregnatriene-3,20-dione-21-yl tri-0-benzoyl-β-D-glucopyranosid)] uronate.

[0003] Several steroid derivatives aimed to reduce toxicity were also synthesized. For example, a sugar-steroid compound capable of specifically reaching the colon was reported (Japanese Patent Laid-open Publication, Sh60-501105 (WO8404041), J. Pharm. Pharmacol. (1991), 43, 353-5, WO9415947 (published on July 21, 1994) and WO9322334 (published on November 11, 1993). Specifically, WO-A-94/15947, which is comprised in the state of the art in the sense of Article 54(3) EPC discloses in Examples 1-4 certain glycosides of steroid compounds belonging to the pregnane series.

[0004] US-A-3,427,300 discloses (in Examples 5 and 6) 21-sugar derivatives of anti-inflammatory steroids which have the hydroxy groups of the 21-sugar group derivatized with O-acetoxy-benzoyl groups, i.e. the hydroxyl groups of the sugar chains are protected with derivatives of acetyl salicylic acid.

[0005] Inventors of the present invention actually synthesized glycosyl steroid derivatives wherein simple sugars or said simple sugars with having hydroxyl groups thereof modified with acetyl groups were linked to steroids, and examined their pharmacological activities, confirming that side-effects of these derivatives were about the same as those of the aglycon steroids, and actually not sufficiently reduced probably because they might be readily hydrolyzed by glucosidases usually omnipresent within living body to release the aglycon steroids.

Disclosure of the Invention

[0006] The present invention was made in view of the aforementioned problems, aiming to provide sugar-steroid compounds with significantly reduced unfavorable side-effects.

[0007] In order to resolve the above-mentioned problems, the present invention features in the modification of hydroxyl groups of simple sugar component of sugar-steroid compounds with sterically bulky protective groups, more specifically, toluoyl (ortho-, meta-, or para-methylbenzoyl), benzoyl, *p*-chlorobenzoyl or arylalkyl (e.g., benzyl) groups.

[0008] By the introduction of these bulky protective groups, the resulting sugar-steroid compounds are rendered more resistant to endogenous glycosidases omnipresent in living body, releasing the active aglycon (steroid) only after the cleavage action of glycosidases which are known to increase at the inflammatory site. Therefore, glycosylsteroid derivatives of the present invention are able to exert anti-inflammatory effect without showing unfavorable side-effects on the non-inflammatory sites. Furthermore, this effect is also achieved by limiting simple sugars to be used to those not present or almost not present in living body (e.g., fucose and rhamnose).

[0009] Accordingly, the present invention provides glycosides of steroid compounds as the aglycon, wherein the 21-position of said steroid compounds is substituted with simple sugars or acylated derivatives of said simple sugars, the hydroxyl groups of said simple sugars or said acylated simple sugars are protected with toluoyl, benzoyl, p-chlorobenzoyl, or aryl-alkyl groups, and said steroid compounds consist of dexamethasone, beta-methasone, the dideacyl derivative of diflupredonate, diflurasone, diflucortolone or betamethasone valerate.

[0010] The present invention also relates to compounds as defined above, for use as an anti-inflammatory agent.

[0011] Further, the present invention relates to glycosides of anti-inflammatory steroid compounds as the aglycon for use as an anti-inflammatory agent, wherein the 21-position of said steroid compounds is substituted with simple sugars or acylated derivatives of said simple sugars, and the hydroxyl groups of said simple sugars or said acylated simple sugars are protected with toluoyl, benzoyl, p-chlorobenzoyl, or aryl-alkyl groups.

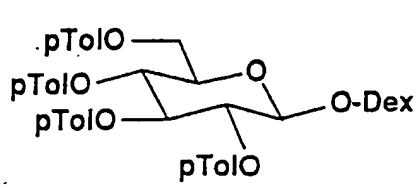
[0012] According to one embodiment, glycosylsteroid derivatives of the present invention are glycosides of dexamethasone as the aglycon, wherein position-21 thereof is substituted with simple sugars or acylated sugars selected from a group comprising glucose, galactose, mannose, fucose, rhamnose, N-acetylglucosamine, N-acetylgalactosamine, galacturonic acid, glucuronic acid and sialic acid.

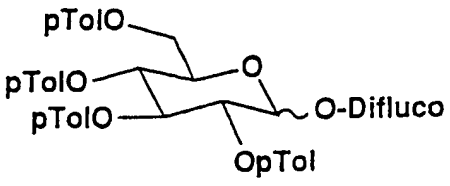
[0013] According to another embodiment, glycosylsteroid derivatives of the present invention are glycosides of bet-

amethasone as the aglycone which are substituted at position-21 thereof with simple sugars or acylated simple sugars selected from a group comprising glucose, galactose, mannose, fucose, N-acetylglucosamine, N-acetylgalactosaimine, galacturonic acid, glucuronic acid and sialic acid.

[0014] Moreover, it is preferred that hydroxyl groups of simple sugars or acylated simple sugars in said glycosides, that is, steroid derivatives of the present invention are protected with toluoyl group.

[0015] In addition, of steroid derivatives related to the present invention, the compounds with the following constitutional formulas are especially useful.





[0016] All anti-inflammatory agents comprising said compounds (glycosides) can be used singly or in combination thereof as dermatological ointment, cream, lotion or tape (liniment for external use only). For the treatment of bronchial asthma and allergic rhinitis, they can be used as the intra-oral and intra-nasal inhalation agents, respectively.

[0017] Steroid derivatives (glycosides) of the present invention mentioned above not only have the activities for suppressing the granuloma growth and crotone oil-induced ear edema, but also less unfavorable side-effects on weights of body, thymus, spleen or adrenal and on leucocyte counts at the administration or painting of them. Therefore, these agents are less toxic and more highly safe as compared with conventional steroid drugs.

[0018] Steroid derivatives of the present invention can be applied for the treatment of eczema, dermatitis (including keratodermia tylodes palmaris progressiva, female facial melanoderma, lichen Vidal, radiodermatitis and dermatitis solaris), pruritus cutaneus, prurigo (including lichen urticatus, strophulus and urticaria perstans), bug bites, psoriasis, palmoplanter pustulosis, lichen planus, lichen nitidus, pityriasis rubra pilaris, pityriasis rosea Gilbert, erythema group (including erythroderma derived from malignant lymphoma), chronic discoid lupus erythematosus, drug rash/toxicoderma, alopecia areata, burn injury (including cicatrix and keloid), frostbite, dermatitis herpetiformis (Duhring) (including psuedosmallpox (permphigoid)), hemorrhoids, and surgical wounds due to tympanoplasty, fenestration operation and tympanomeatomastoidectomy.

[0019] The aforementioned protected compounds (glycosides) may be prepared by first protecting the starting material simple sugars or acylated simple sugars with toluoyl or acetyl group, replacing position-1 thereof with a halogen atom, and then reacting the sugar halide with dexamethasone or betamethasone in the presence of molecular sieve and Lewis acids such as silver carbonate, silver triflate or tin (VI) chloride. Said compounds (glycosides) may be obtained by deprotecting these protected glycosides with MeONa/MeOH of the like.

[0020] In this case, the use of toluoyl group as the protecting group is advantageous, because said group not only provides the requested product in a better yield by preventing the formation of undesirable ortho ester, but also the toluoyl-protected derivatives themselves have lower undesirable side-effects and higher pharmacological safety.

Brief description of drawings

[0021]

Fig. 1 is a flow-chart showing the synthesis route of glucosyldexamethasone.
Fig. 2 is a flow-chart showing the synthesis route of glucosyldexamethasone (ortho ester derivative).
Fig. 3 is a flow-chart showing the synthesis route of galactosyldexamethasone.
Fig. 4 is a flow-chart showing the synthesis route of mannosyldexamethasone.
Fig. 5 is a flow-chart showing the synthesis route of β-N-acetylglucosaminyldexamethasone.
Fig. 6 is a flow-chart showing the synthesis route of N-acetylgalactosaminyldexamethasone.
Fig. 7 is a flow-chart showing the synthesis route of β-glucuronyldexamethasone and Tol-protected derivative of β-glucuronyldexamethasone.
Fig. 8 is a flow-chart showing the synthesis route of β-galacturonyldexamethasone and Tol-protected derivative of β-galacturonyldexamethasone.
Fig. 9 is a flow-chart showing the synthesis route of β-fucosyldexamethasone.
Fig. 10 is a flow-chart showing the synthesis route of sodium salt of sialyldexamethasone.

Fig. 11 is a flow-chart showing the synthesis route of sialylbetamethasone.
Fig. 12 is a flow-chart showing the synthesis route of per-Tol-protected derivative of glucosylbetamethasone.
Fig. 13 is a flow-chart showing the synthesis route of glucosylbetamethasone (*p*-toluoyl derivative).
Fig. 14 is a flow-chart showing the synthesis route of glucosylbetamethasone (*o*-toluoyl derivative).
Fig. 15 is a flow-chart showing the synthesis route of glucosylbetamethasone (*m*-toluoyl derivative).
Fig. 16 is a flow-chart showing the synthesis route of glucosylbetamethasone (benzoyl derivative).
Fig. 17 is a flow-chart showing the synthesis route of glucosylbetamethasone (benzyl derivative).
Fig. 18 is a flow-chart showing the synthesis route of glucosyldiflupredonate (*p*-toluoyl derivative).
Fig. 19 is a flow-chart showing the synthesis route of glucosyldiflorasone (*p*-toluoyl derivative).
Fig. 20 is a flow-chart showing the synthesis route of glucosyldiflucortolone (*p*-toluoyl derivative).
Fig. 21 is a flow-chart showing the synthesis route of glucosyldiflucortolone (benzoyl derivative).
Fig. 22 is a flow-chart showing the synthesis route of glucosyldiflucortolone (*p*-chlorobenzoyl derivative).
Fig. 23 is a flow-chart showing the synthesis route of glucosyldiflucortolone (acetyl derivative).
Fig. 24 is a flow-chart showing the synthesis route of glucosyldexamethasone (acetyl derivative).
Fig. 25 is a flow-chart showing the synthesis route of galactosyldexamethasone (acetyl derivative).
Fig. 26 is a flow-chart showing the synthesis route of glucosylbetamethasone valerate (*m*-toluoyl derivative).
Fig. 27 is a flow-chart showing the synthesis route of β-rhamnosyldexamethasone.

Most preferred embodiment for practicing the present invention

[0022] The most preferred embodiments of the present invention will be described below.

1) Synthesis of compounds

[0023] Syntheses of derivatives of dexamethasone and betamethasone are described below. Unless otherwise noted, chemicals used of the reagent grade were purchased from Tokyo Kasei Kogyo Co., LTD.

Example 1

Synthesis of glucosyldexamethasone (Fig. 1)

1) Toluoylation of glucose

[0024] D-(+)-glucose 1 (2 g) was dissolved in chloroform (40 ml), and to this solution were added *p*-toluoyl chloride (14.5 ml) and pyridine (8.9 ml) drop-wise at 0 - 5°C. While the reaction temperature was slowly raised to room temperature, the mixture was stirred for 6 h. The reaction solution was poured into ice-water and extracted with chloroform. The organic layer was washed successively with saturated solutions of copper sulfate, sodium bicarbonate, and sodium chloride. After the chloroform solution was dried over anhydrous magnesium sulfate, the solvent was distilled off *in vacuo*. A portion (5.33 g) of the residue thus obtained was purified by silica gel column chromatography (toluene:ethyl acetate = 50:1) to give 2 (4.5 g) as white powder.

Compound 2

[0025]

$C_{46}H_{42}O_{11}$ MW = 770.831
^{1}H-NMR [500 MHz, $CDCl_3$, Ref = 0.000ppm(TMS)]

$(CH_3C_6\underline{H}_4CO\text{-})$ X 5 : 8.062, 7.910, 7.834, 7.780, 7.775 (each 2H, d, J = 8.06)
7.341, 7.207, 7.156, 7.106, 7.101 (each 2H, d, J = 8.06)
$(C\underline{H}_3C_6H_4CO\text{-})$ x 5 : 2.474, 2.408, 2.362, 2.315, 2.309 (each 3H, s)

2) Bromination of glucose

[0026] 2 (4.5 g) was dissolved in chloroform (20 ml), and to this solution was added hydrobromic acid-acetic acid

solution (8.8 ml) at 0 - 5°C. While the reaction temperature was slowly raised to room temperature, the mixture was stirred at room temperature overnight. After the unreacted bromine was removed with an argon stream, the solvent was distilled off *in vacuo*. The residue was dissolved in chloroform, and washed with cold saturated sodium bicarbonate solution. After the chloroform solution was dried over anhydrous magnesium sulfate, the solvent was distilled off *in vacuo* to yield 3 as pale yellow powder [2.5 g (yield 59.2%)].

Compound 3

[0027]

$C_{38}H_{35}O_9Br$ MW = 715.593
^{1}H-NMR [500 MHz, $CDCl_3$, Ref = 0.000ppm(TMS)]

$(CH_3C_6\underline{H}_4CO-)$ x 4 :	7.944, 7.881, 7.830, 7.761 (each 2H, d, J = 8.06)
	7.236, 7.191, 7.160, 7.094 (each 2H, d, J = 8.06)
$(C\underline{H}_3C_6H_4CO-)$ x 4 :	2.414, 2.365, 2.357, 2.299 (each 3H, s)
Position-1 of glucose :	6.849 (1H, d, $J_{1,2}$ = 4.03)

3) Synthesis of glucosyldexamethasone

[0028] Dexamethasone (6) (300 mg) was dissolved in tetrahydrofuran (20 ml), and to this solution were added molecular sieve 5A (400 mg) and silver triflate (390 mg). Then, to this mixture was added, under an argon atmosphere and at 0 - 5°C, a glucose bromide (3) (1.10 g) dissolved in tetrahydrofuran (10 ml). While the reaction temperature was slowly raised to room temperature, the resulting mixture was stirred for 2 h. After the reaction solution was filtered, the solvent of the mother liquor was evaporated *in vacuo*. The residue thus obtained was dissolved in chloroform, and washed with saturated sodium chloride solution. After the chloroform solution was dried over anhydrous magnesium sulfate, the solvent was distilled off *in vacuo*. The residue thus obtained was purified by silica gel column chromatography (toluene:ethyl acetate = 3:1) to obtain 4 as white powder [441.2 mg (yield 55.7%)].

[0029] This product was further purified by HPLC using a reversed phase partition column (acetonitrile-water) to obtain β-anomer (4β) [248.16 mg (yield 32.3%)] and α-anomer (4α) [52.84 mg (yield 6.7%)], respectively, both as white powder.

Compound 4

[0030]

$C_{60}H_{63}FO_{14}$ MW = 1027.148

β-anomer (4β)

[0031]

^{1}H-NMR [500 MHz, $CDCl_3$, Ref = 0.000 ppm (TMS)]
1 : 5.040 (1H, d, $J_{1,2}$ = 8.06)
2 : 5.492 (1H, d, $J_{2,3}$ = 9.89)
3 : 5.884 (1H, t, $J_{3,4}$ = 10.99)
4 : 5.660 (1H, t)
5 : 4.064 - 4.044 (1H, m)
6 : 4.643 (2H, t)

$(C\underline{H}_3C_6H_4CO-)$ x 4 :	2.405, 2.363, 2.351, 2.299 (each 3H, s)
$(CH_3C_6\underline{H}_4CO-)$ x 4 :	7.873, 7.831, 7.808, 7.732 (each 2H, d, J = 6.9 Hz)

IR ν^{KBr} cm^{-1} 3508(O-H), 1734(C=O position-20), 1665(C=O position-3)
FAB(+)MS 1027$(M+H)^+$, 1009$(M-OH)^+$
MP : 152 - 155°C

α-anomer (4α)

[0032]

1 : 5.302 (1H, d, $J_{1,2}$ = 3.67)
3 : 6.215 (1H, t)
4 : 5.727 (1H, t)
5 : 4.631 - 4.605 (1H, m)
6 : 4.867 (1H, dd, $J_{6,6'}$ = 12.46)
6': 4.276 (1H, dd)

($C\underline{H}_3C_6H_4CO$-) x 4 : 2.410, 2.367, 2.348, 2.300 (each 3H, s)
($CH_3C_6\underline{H}_4CO$-) x 4 : 7.899, 7.864, 7.853, 7.768 (each 2H, d)

IR ν^{KBr} cm^{-1} 3438(O-H), 1731(C=O position-20), 1666(C=O position-3)
FAB(+)MS 1027$(M+H)^+$, 1009$(M-OH)^+$
MP : 150 - 153°C

4) Deprotection of glucosyldexamethasone (β-anomer)

[0033] 4β (144 mg) was dissolved in methanol (16 ml), and to this solution was added, at 0 - 5°C, 1 M sodium methoxide (107.6 µl). The resulting mixture was stirred for 5 h at room temperature. The reaction solution was applied to a gel filtration column of LH-20, and eluted with methanol. After the solvent of fractions containing product was distilled off *in vacuo*, the residue thus obtained was purified by HPLC using a reversed phase partition column (acetonitrile-water) to obtain 5β as white powder [67.8 mg (yield 88.5%)].

Compound 5β

[0034]

$C_{28}H_{39}FO_{10}$ MW = 554.608
^{1}H-NMR [(500 MHz, d6-DMSO, Ref = 2.50ppm(DMSO)]
1 ; 4.170 (1H, d, $J_{1,2}$ = 7.70)
5 ; 3.438 (1H, dd, $J_{5,6}$ = 12.09)
6 ; 3.696 (1H, dd, $J_{6,6'}$ = 1.83)
FAB(-)MS 553$(M-H)^+$
MP : 238 - 241°C

5) Deprotection of glucosyldexamethasone (α-anomer)

[0035] 4α (35 mg) was dissolved in methanol (10 ml), and to this solution was added 1 M sodium methoxide (62 µl) at 0 - 5°C. The resulting mixture was stirred for 5 h at room temperature. The reaction mixture was loaded onto a gel filtration column of LH-20, and eluted with methanol. After the solvent of fractions containing product was distilled off *in vacuo*, the residue thus obtained was purified by HPLC using a reversed phase partition column (acetonitrile-water) to obtain 5α as white powder [7.46 mg (yield 40.0%)].

Compound 5α

[0036]

$C_{28}H_{39}FO_{10}$ MW = 554.608
IR ν^{KBr} cm^{-1} 3404(O-H), 1712(C=O position-20), 1661(C=O position-3)

FAB(-)MS 553$(M-H)^+$
MP : 173 - 176°C

Example 2

Synthesis of glucosyldexamethasone (ortho ester)(Fig. 2)

1) Bromination of glucose (per Ac derivative)

[0037]

$$C_{16}H_{22}O_{11}(8) \rightarrow C_{14}H_{19}O_9Br(9)$$

(MW = 390.34) (MW = 411.20)

[0038] To hydrogen bromide-acetic acid solution (80 ml) pre-cooled to 0 - 5°C was added pentaacetyl-β-D-glucose (8) (20 g), and the mixture was stirred for 3 h at the same temperature. Then, after the solvent was distilled off *in vacuo*, the residue was dissolved in chloroform, and the solution was washed with saturated sodium bicarbonate solution. After the chloroform solution was dried over anhydrous magnesium sulfate, the solvent was evaporated *in vacuo*. The residue thus obtained was recrystallized from ethyl alcohol (60 ml) to obtain 9 as white powder [12.0 g (yield 56.7%)].

^{1}H-NMR [500 MHz, $CDCl_3$, Ref = 0.000ppm(TMS)]
1 : 6.612 (1H, d, $J_{1,2}$ = 4.03)
2 : 4.842 (1H, dd, $J_{2,3}$ = 9.89)
3 : 5.562 (1H, t)
4 : 5.163 (1H, t)
5 : 4.292 (1H, dd, $J_{5,6}$ = 4.03)
6 : 4.332 (1H, dd, $J_{6,6'}$ = 12.45)
6': 4.122 (1H, dd)
(-OCOCH_3) x 4 : 2.103, 2.099, 2.082, 2.036 (each 3H, s)

2) Synthesis of glucosyldexamethasone (ortho ester)

[0039]

$$C_{14}H_{19}O_9Br(9) + \text{dexamethasone}(6) \rightarrow C_{36}H_{47}O_{11}F(10)$$

(MW = 411.20) (MW = 674.8)

[0040] Dexamethasone (6) (1.7 g) was dissolved in chloroform (300 ml), and to this solution were added molecular sieve 4A (5 g) and silver carbonate (5.5 g). To this solution was added, under a nitrogen atmosphere, a glucose bromide (9, 5 g) dissolved in chloroform (150 ml), and the mixture was stirred for 4 h. After the reaction solution was filtered, the filtrate was washed with saturated sodium chloride solution. After the chloroform solution was dried over anhydrous magnesium sulfate, the solvent was distilled off *in vacuo*. The residue thus obtained was purified by silica gel column chromatography first with a solvent system (chloroform:methanol = 30:1), and then with another solvent system (toluene:ethyl acetate = 2:1) to obtain (10) as white powder [193.8 mg (yield 43.5%)].

Compound 10

[0041]

Rf = 0.56 (silica gel TLC, $CHCl_3$: CH_3OH = 30 : 1)

^{1}H-NMR [500 MHz, $CDCl_3$, Ref = 0.000ppm(TMS)]
1 : 5.786 (1H, d, $J_{1,2}$ = 5.13)
(-OCOC$\underline{H_3}$) x 4 : 2.142, 2.115, 2.111 (12H, s)

Example 3

Synthesis of galactosyldexamethasone (Fig. 3)

1) Toluoylation of galactose (11 → 12)

[0042] D-(+)galactose (11) (2 g) was dissolved in chloroform (40 ml), and to this solution were added *p*-toluoyl chloride (14.5 ml) and pyridine (8.9 ml) drop-wise at 0 - 5°C. While the reaction temperature was raised slowly to room temperature, the mixture was stirred for 5 h. After the reaction solution was poured into ice-water and extracted with chloroform, the organic layer was washed successively with saturated solutions of copper sulfate, sodium bicarbonate and sodium chloride. After the chloroform solution was dried over anhydrous magnesium sulfate, the solvent was distilled off *in vacuo*. A portion (5 g) of the residue thus obtained was purified by silica gel column chromatography (toluene:ethyl acetate = 40:1) to obtain 12 as white powder [2.4 g (yield 97.4%)].

Compound 12

[0043]

$C_{46}H_{42}O_{11}$ MW = 770.831
^{1}H-NMR [500 MHz, $CDCl_3$, Ref = 0.000ppm(TMS)]

$CH_3C_6\underline{H_4}CO$- : 8.000, 7.985, 7.837, 7.740, 7.696
(each 2H, d, J = 8.43)
$C\underline{H_3}C_6H_4CO$- : 2.452, 2.449, 2.372, 2.305, 2.298
(each 3H, S)

2) Bromination of 12 (12 → 13)

[0044] 12 (2.35 g) was dissolved in chloroform (10 ml), and to this solution was added hydrogen bromide-acetic acid solution (4.58 ml) at 0 - 5°C. While the reaction temperature was slowly raised to room temperature, the mixture was stirred overnight. After removing the unreacted bromine with an argon stream, the solvent was distilled off *in vacuo*. The residue was taken up into chloroform, and washed with cold saturated sodium bicarbonate solution. After dried over anhydrous magnesium sulfate, the solvent was distilled off *in vacuo* to obtain 13 as pale yellow powder [1.87 g (yield 83.7%)].

Compound 13

[0045]

$C_{38}H_{35}O_9Br$ MW = 715.593
^{1}H-NMR [500 MHz, $CDCl_3$, Ref = 0.00ppm (TMS)]
1 : 6.963 (1H, d, $J_{1,2}$ = 4.03)
2 : 5.614 (1H, dd, $J_{2,3}$ = 10.63)
3 : 6.018 (1H, dd, $J_{3,4}$ = 3.29)
4 : 6.068 (1H, dd)
5 : 4.883 (1H, t)
6 : 4.598 (1H, dd, $J_{6,6'}$ = 11.72)
6': 4.424 (1H, dd)

$CH_3C_6\underline{H_4}CO$- : 7.946, 7.896, 7.880, 7.676
7.278, 7.213, 7.185, 7.050
(each 2H, d, J = 8.06)
$C\underline{H_3}C_6H_4CO$- : 2.444, 2.394, 2.360, 2.302
(each 3H, s)

3) Synthesis of galactosyldexamethasone

$$13 + 6 \rightarrow 14\alpha + 14\beta$$

[0046] Dexamethasone 6 (456 mg) was dissolved in tetrahydrofuran (20 ml), and to this solution were added molecular sieve 5A (700 mg) and silver triflate (598 mg). To this solution was added, under an argon atmosphere, a galactose bromide 13 (1.7 g) dissolved in tetrahydrofuran (20 ml), and the mixture was stirred at room temperature for 2 - 3 h. After the reaction solution was filtered, the solvent was distilled off from the mother liquor *in vacuo*. The residue was dissolved in ethyl acetate, washed with saturated sodium chloride solution, and dried over anhydrous magnesium sulfate. The solvent was distilled off *in vacuo*, and the residue thus obtained was first purified by silica gel chromatography (toluene:ethyl acetate = 3:1). The product was further purified by HPLC using a reversed phase partition column (acetonitrile-water) to obtain β-anomer (14β) [232.2 mg (yield 31.2%)] and α-anomer (14α) [178.6 mg (yield 24.0%)], both as white powder.

Compound 14

[0047]

$C_{60}H_{63}FO_{14}$ MW = 1027.148

β-anomer (14β)

[0048]

^{1}H-NMR(500 MHz, $CDCl_3$, Ref = 0.00ppm (TMS))
1 : 4.947 (1H, d, $J_{1,2}$ = 8.06)
2 : 5.829 (1H, dd, $J_{2,3}$ = 10.26)
3 : 5.572 (1H, dd, $J_{3,4}$ = 3.30)
4 : 5.906 (1H, d)

$CH_3C_6\underline{H}_4CO$- : 7.991, 7.879, 7.876, 7.658, 7.292, 7.240, 7.168, 7.040 (each 2H, d, J = 8.06)
$C\underline{H}_3C_6H_4CO$- : 2.426, 2.414, 2.346, 2.292 (each 3H, s)

IR ν^{KBr} cm^{-1} 3496(O-H), 1731(C=O position-20), 1666(C=O position-3)
FAB(+)MS 1027$(M+H)^+$, 1009$(M-OH)^+$
MP : 163 - 165°C

α-anomer (14α)

[0049]

1 : 5.438 (1H, d, $J_{1,2}$ = 3.66)
2 : 5.666 (1H, dd, $J_{2,3}$ = 10.26)
5 : 4.548 (1H, dd, $J_{5,6}$ = 5.13, $J_{5,6'}$ = 7.69)
6 : 4.695 (1H, dd, $J_{6,6'}$ = 10.99)
6' : 4.308 (1H, dd)

$CH_3C_6\underline{H}_4CO$- : 8.002, 7.883, 7.835, 7.667, 7.295, 7.192, 7.157, 7.015 (each 2H, d, J = 8.06)
$C\underline{H}_3C_6H_4CO$- : 2.457, 2.387, 2.341, 2.294 (each 3H, s)

IR ν^{KBr} cm^{-1} 3460(O-H), 1730(C=O position-20), 1666(C=O position-3)
FAB(+)MS 1027$(M+H)^+$, 1009$(M-OH)^+$
MP : 163 - 165°C

4) Deprotection of galactosyldexamethasone (β) (14β → 15β)

[0050] 14β (160 mg) was dissolved in methanol (15 ml), and to this solution was added 1 M sodium methoxide (121 µl) at 0 - 5°C. The mixture was stirred for 3 h at room temperature. The reaction solution was loaded onto a gel filtration column of LH-20, and eluted with methanol. After the solvent was distilled off from fractions containing product *in vacuo*, the residue thus obtained was purified by HPLC using a reversed phase partition column (acetonitrile-water) to obtain 15β as white powder [67.9 mg (yield 78.6%)].

Compound 15

[0051]

$C_{28}H_{39}FO_{10}$ MW = 554.608
^{1}H-NMR [(500 MHz, CD_3OD, Ref = 3.30ppm (CH_3OD)]
1 : 4.236 (1H, d, $J_{1,2}$ = 7.69)
2 : 3.593, 3.424 (1H, dd, $J_{2,3}$ = 9.89)
3 : 3.476, 3.456 (1H, dd, $J_{3,4}$ = 3.30)
4 : 3.795 (1H)
5 : 3.505, 3.492 (1H, dd, $J_{5,6}$ = 6.96, $J_{5,6}$ = 4.76)
6 : 3.774, 3.752 (1H, dd, $J_{6,6'}$ = 11.35)
6': 3.719, 3.697 (1H, dd)
FAB(-)MS 553$(M-H)^+$
MP : 175 - 178°C

5) Deprotection of galactosyldexamethasone (α) (14α → 15α)

[0052] 14α (127.05 mg) was dissolved in methanol (10 ml), and to this solution was added 1 M sodium methoxide (96 µl) at 0 - 5°C. The mixture was stirred at room temperature for 3 h. The reaction mixture was applied to a gel filtration column of LH-20, and eluted with methanol. After the solvent was distilled off from fractions containing product *in vacuo*, the residue thus obtained was purified by HPLC using a reversed phase partition column (acetonitrile-water) to obtain 15α as white powder [49.19 mg (yield 72.8%)].

Compound 15

[0053]

$C_{28}H_{39}FO_{10}$ MW = 554.608
^{1}H-NMR [(500 MHz, CD_3OD, Ref = 3.30ppm (CH_3OD)]
1 : 3.885 (1H, d, $J_{1,2}$ = 2.93)
2 - 6 : 3.6 - 3.8 ppm(6H, m)
IR ν^{KBr} cm^{-1} 3438(O-H), 1715(C=O position-20), 1662(C=O position-3)
FAB(-)MS 553$(M+H)^+$
MP : 225 - 228°C

Example 4

Synthesis of mannosyldexamethasone (Fig. 4)

1) Toluoylation of mannose

[0054] D-(+)-Mannose 21 (2.3 g) was dissolved in chloroform (40 ml), and to this solution were added *p*-toluoyl chloride (14.5 ml) and pyridine (8.9 ml) drop-wise at 0 - 5°C. While the reaction temperature was slowly raised to room temperature, the mixture was stirred for 5 h. The reaction solution was poured into ice-water, and extracted with chloroform. The organic layer was washed successively with saturated solutions of copper sulfate, sodium bicarbonate, and sodium chloride. After the chloroform solution was dried over anhydrous magnesium sulfate, the solvent was distilled off *in vacuo*. A portion (6 g) of the residue thus obtained was purified by silica gel column chromatography (toluene:ethyl acetate = 40:1) to give 22 as white powder [3.18 g (yield 88.7%)].

Compound 22

[0055]

$C_{46}H_{42}O_{11}$
^{1}H-NMR [500 MHz, $CDCl_3$, Ref = 0.000ppm(TMS)]

$(CH_3C_6\underline{H}_4CO\text{-})$ x 5 :	8.078, 7.961, 7.950, 7.834, 7.738, 7.345, 7.195, 7.178, 7.151, 7.077 (each 2H, d, J = 8.06)
$(C\underline{H}_3C_6H_4CO\text{-})$ x 5 :	2.476, 2.449, 2.423, 2.350, 2.306 (each 3H, s)
Position-1 of mannose :	6.579 (1H, d, $J_{1,2}$ = 1.84)

2) Bromination of mannose derivative (22)

[0056] 22 (3.14 g) was dissolved in chloroform (15 ml), and to this solution was added hydrogen bromide-acetic acid solution (6.12 ml) at 0 - 5°C. While the reaction temperature was slowly raised to room temperature, the mixture was stirred at room temperature overnight. After the unreacted bromine was removed with an argon stream, the solvent was distilled off *in vacuo*. The residue was dissolved in chloroform, and washed with cold saturated sodium bicarbonate solution. After the chloroform solution was dried over anhydrous magnesium sulfate, the solvent was distilled off *in vacuo* to give 23 as light yellow powder [2.61 g (yield 87.6%)].

Compound 23

[0057]

$C_{38}H_{35}O_9Br$ MW = 715.593
^{1}H-NMR [500 MHz, $CDCl_3$, Ref = 0.000ppm(TMS)]

$(CH_3C_6\underline{H}_4CO\text{-})$ x 4 :	7.972, 7.897, 7.858, 7.719 (each 2H, d, J = 8.06)
$(C\underline{H}_3C_6H_4CO\text{-})$ x 4 :	2.430, 2.359, 2.294 (12H, s)

3) Synthesis of mannosyldexamethasone

[0058] Dexamethasone (6) (600 mg) was dissolved in tetrahydrofuran (20 ml), and to this solution were added molecular sieve 5A (600 mg) and silver triflate (783 mg). To this mixture was added, under an argon atmosphere, a mannose bromide 23 (2.3 g) dissolved in tetrahydrofuran (15 ml), and the reaction mixture was stirred for 4 h until the reaction temperature reached room temperature. The reaction solution was filtered, and the solvent of the mother liquor was distilled off *in vacuo*. The residue thus obtained was dissolved in ethyl acetate, washed with saturated sodium chloride solution, and then the organic layer was dried over anhydrous magnesium sulfate. After the solvent was distilled off *in vacuo*, the residue thus obtained was purified by silica gel column chromatography (toluene:ethyl acetate = 3:1) to obtain 647 mg of white powder.

[0059] The above product was further purified by HPLC using a reversed phase partition column (acetonitrile-water) to obtain α-anomer (24α) [462.3 mg (yield 29.2%)].

Compound 24α

[0060]

$C_{60}H_{63}FO_{14}$ MW = 1027.148
^{1}H-NMR [500 MHz, CD Cl_3, Ref = 0.00ppm (TMS)]
1 : 5.216 (1H, s)
2 : 5.954 (1H, dd , $J_{2,3}$ = 3.29)
3 : 6.153 (1H, dd , $J_{3,4}$ = 10.25)
6' : 4.456 (1H, dd , $J_{6,6'}$ = 12.09)

($CH_3C_6\underline{H}_4CO$-) x 4 : 8.183, 8.099, 8.007, 7.935
(each 2H, d, J = 8.06)
($C\underline{H}_3C_6H_4CO$-) x 4 : 2.646, 2.612, 2.577, 2.508
(each 3H, s)

IR ν^{KBr} cm^{-1} 3498(O-H), 1730(C=O position-20), 1667(C=O position-3)
FAB(+)MS 1027$(M+H)^+$, 1009$(M-OH)^+$
MP : 155 - 158°C

4) Deprotection of mannosyldexamethasone (α)

[0061] 24α (150 mg) was dissolved in methanol (10 ml), and to this solution was added 1 M sodium methoxide (113 µl) at 0 - 5°C. The mixture was stirred at room temperature for 2 h. The reaction solution was applied to a gel filtration column of LH-20, and eluted with methanol. After evaporation of the solvent from fractions containing product *in vacuo*, the residue was purified by HPLC using a reversed phase partition column (acetonitrile-water) to obtain 25α as white powder [57.67 mg (yield 72.3%)].

Compound 25α

[0062]

$C_{28}H_{39}FO_{10}$ MW = 554.608
^{1}H-NMR [500 MHz, DMSO, Ref = 2.50ppm (DMSO)]
1 : 4.625 (1H, d, $J_{1,2}$ = 1.83)
2 : 3.707 (1H, d, $J_{2,3}$ = 3.30)
4 : 3.403 (1H)
6 : 3.647 (1H, dd, $J_{6,6'}$= 11.73)
IR ν^{KBr} cm^{-1} 3438(O-H), 1715(C=O position-20), 1662(C=O position-3)
FAB(-)MS 553$(M+H)^+$
MP : 189 - 192°C

5) Acetylation of mannose

[0063]

$C_6H_{12}O_6$ (21) → $C_{16}H_{22}O_{11}$ (27)

(MW = 180.16) (MW = 390.34)

[0064] D-(+)Mannose 21 (15 g) was suspended in acetic anhydride (180 ml), and to this suspension was added pyridine (46.5 ml) drop-wise at 0 - 5°C. The mixture was stirred at room temperature for about 5 h. The reaction solution was poured into ice-water, extracted with chloroform, and the organic layer was washed with 5% copper sulfate solution. After the chloroform solution was dried over anhydrous magnesium sulfate, the solvent was evaporated *in vacuo* to give 27 as pale yellow oily product (36.9 g).

^{1}H-NMR [500 MHz, $CDCl_3$, Ref = 0.000ppm(TMS)]
1 : 6.091 (1H, d, $J_{1,2}$ = 1.83)
6 : 4.332 (1H, dd, $J_{6,6'}$= 12.46)
6': 4.122 (1H, dd , $J_{5,6'}$= 2.57)

(-OCOC$\underline{H}_3$) x 5 : 2.181, 2.171, 2.096, 2.057, 2.011
(each 3H, s)

6) Bromination of mannose

[0065]

27	→	28
$C_{16}H_{22}O_{11}$		$C_{14}H_{19}O_9Br$
(MW = 390.34)		(MW = 411.20)

[0066] 27 (5.8 g) was dissolved in chloroform (11 ml), and to this solution was added a hydrobromide-acetic acid solution (11 ml) at 0 - 5°C. The mixture was stirred for about 4 h. The reaction solution was washed with saturated sodium bicarbonate solution, dried over anhydrous magnesium sulfate. Evaporation of the solvent *in vacuo* gave 28 as pale yellow oily product [5.9 g (yield 95.9%)].

^{1}H-NMR [500 MHz, $CDCl_3$, Ref = 0.000ppm(TMS)]
1 : 6.298 (1H, d, $J_{1,2}$ = 1.10)
2 : 5.451 (1H, dd, $J_{2,3}$ = 3.30)
3 : 5.720 (1H, dd , $J_{3,4}$ = 10.26)
4 : 5.372 (1H, t)
5 : 4.226 (1H, ddd, $J_{5,6}$ = 4.76)
6 : 4.332 (1H, dd , $J_{6,6'}$ = 12.45)
6': 4.144 (1H, dd, $J_{5,6'}$ = 2.20)
(-OCOCH_3) x 4 : 2.178, 2.108, 2.077, 2.012 (each 3H, s)

7) Synthesis of mannosyldexamethasone (per Ac derivative)

[0067]

$C_{14}H_{19}O_9Br$ (28) + dexamethasone (6)	→	$C_{36}H_{47}FO_{14}$ (29)
(MW = 411.20)		(MW = 722.76)

[0068] Dexamethasone 6 (1.7 g) was dissolved in chloroform (300 ml), and to this solution were added molecular sieve 4A (5 g) and silver carbonate (5.5 g). To this mixture was added, under a nitrogen atmosphere, a mannose bromide 28 (5.8 g) dissolved in chloroform (150 ml), and stirred at room temperature overnight. After the reaction solution was filtered, the mother liquor was washed with saturated sodium chloride solution and dried over anhydrous magnesium sulfate. After the solvent was distilled off *in vacuo*, the residue thus obtained was purified by silica gel column chromatography first with (chloroform:methanol = 30:1) and further purified by the same system with (toluene:ethyl acetate = 2:1) to obtain 29 as white powder [453.7 mg (yield 49.6%)].

^{1}H-NMR [500 MHz, $CDCl_3$, Ref = 0.000ppm(TMS)]
1 : 5.529 (1H, d, $J_{1,2}$ = 2.93)
2 : 4.860 (1H, dd, $J_{2,3}$ = 4.40)
3 : 5.034 (1H, dd , $J_{3,4}$ = 9.90)
4 : 5.295 (1H, t, $J_{4,5}$ = 9.52)
5 : 3.709 (1H, ddd, $J_{5,6}$ = 5.47)
6 : 4.309 (1H, dd, $J_{6,6'}$ = 12.45)
6' : 4.122 (1H, dd , $J_{5,6'}$ = 2.57)
(-OCOCH_3) x 4 : 2.110, 2.077, 2.072, 1.801 (each 3H, s)
FAB(+)MS 723$(M+H)^+$

8) Deacetylation of mannosyldexamethasone

[0069]

$C_{36}H_{47}FO_{14}$ (29) → $C_{28}H_{39}FO_{10}$ (25α)

(MW = 722.76) (MW = 554.61)

[0070] 5 (108.24 mg) was dissolved in methanol (25 ml), and to this solution was added 1 M sodium methoxide (1.25 ml) at 0 - 5°C. The mixture was stirred at room temperature for 6 h. The reaction solution was applied to a gel filtration column of LH-20 and eluted with methanol. The solvent was distilled off from fractions containing product *in vacuo* to give 25α as white powder [81.4 mg (yield 97.8%)].

Example 5

Synthesis of β-N-acetylglucosaminyldexamethasone (Fig. 5)

1) Synthesis of N-acetylglucosaminyl chloride (31 → 33)

[0071] N-Acetylglucosamine 31 [10 g (45.2 mmol)] was suspended in acetyl chloride (20 ml), and stirred at room temperature overnight. The reaction solution was diluted with chloroform (100 ml), and poured into ice-water. The chloroform layer was washed with saturated sodium bicarbonate solution, dried over anhydrous magnesium sulfate, and the solvent was distilled off *in vacuo*. The residue thus obtained was dissolved in diethyl ether (about 100 ml), and allowed to stand at -30°C overnight. Pale yellow powder (33) which precipitated was collected by filtration [12.7 g (yield 76.8%)].

Compound 33

[0072]

$C_{14}H_{20}ClNO_8$ MW = 365.77
MP : 123 - 126°C (decomp.)
FAB(+)MS 364$(M-H)^+$, 366$(M+H)^+$
^{1}H-NMR (500 MHz, $CDCl_3$, Ref = 0.000ppm(TMS))

δ;	1.991, 2.058, 2.060, 2.110 (each 3H, 3OAc+NHAc)
	4.141 (1H, dd , J = 1.8, 12.1Hz, H-6)
	4.307 -4.254 (2H, m, H-5,6')
	4.538 (1H, ddd, J = 3.7, 8.8, 10.6Hz, H-2)
	5.221 (1H, t, J = 9.9 Hz, H-4)
	5.325 (1H, t, J = 10.6Hz, H-3)
	5.811 (1H, d, J = 8.8 Hz, NHAc)
	6.193 (1H, d, J = 3.7 Hz, H-1)
IR ν^{KBr} cm^{-1} :	3245(NH), 1742($OCOCH_3$)
	1644($NHCOCH_3$)

2) Synthesis of a protected derivative of N-acetylglucosaminyldexamethasone

33 + dexamethasone (6) → 34

[0073] An N-acetylglucosamine chloride 33 [2.8 g (7.66 mmol)] and dexamethasone 6 [1.6 g (2.55 mmol)] were suspended in α-methylstyrene, and the suspension was stirred at 80 - 90°C for 5 h. The reaction solution was diluted with chloroform, filtered to remove insoluble materials, and the filtrate was evaporated to dryness *in vacuo*. The residue thus obtained was purified by silica gel column chromatography, eluted first with (chloroform:methanol = 20:1) and then with (toluene:ethyl acetate = 1:3) to give 34 as pale yellow powder [114.2 mg (yield 6.2%)]. The powder was dissolved in a small amount of ethyl acetate, and allowed to stand at -30°C for 3 days. Precipitated crystals were collected by fil-

tration, weighing 81.4 mg (white powder).

Compound 34

[0074]

$C_{36}H_{48}FNO_{13}$ MW = 721.77
MP : 251°C
FAB(+)MS 704 $(M-H_2O)^+$, 722 $(M+H)^+$,
744 $(M+Na)^+$

IR ν^{KBr} cm^{-1} : 3350(OH), 1750($OCOCH_3$)
1730, 1662(C=O), 1620, 1603(C=C)

^{1}H-NMR (500 MHz, $CDCl_3$, Ref = 0.000ppm(TMS)

δ ; 0.883 (3H, d, J = 7.3 Hz, 16-CH_3)
0.964 (3 H, s, CH_3)
1.560 (3 H, s, CH_3)
1.949, 2.041, 2.043, 2.106 (3H, 4s, 3OAc+NHAc)
3.713 (1H, ddd, J = 2.9, 4.8, 9.5 Hz, H-5_{GlcNAc})
3.818 (1H, dd, J = 8.4, 10.3Hz, H-2_{GlcNAc})
4.160 (1H, dd, J = 2.9, 12.1Hz, H-6_{GlcNAc})
4.329 (1H, dd, J = 4.8, 12.1Hz, H' -6_{GlcNAc})
4.480 (1H, d, J = 18.0Hz, H-21)
4.735 (1H, d, J = 18.0Hz, H' -21)
4.840 (1H, d, J = 8.4 Hz, H-1_{GlcNAc})
5.046 (1H, t, J = 9.5 Hz, H-4_{GlcNAc})
5.304 (1H, dd, J =9.5, 10.3Hz, H-3_{GlcNAc})
6.116 (1H, s, H-4)
6.340 (1H, dd, J = 1.8, 9.9 Hz, H-1)
7.283 (1H, d, J = 9.9 Hz, H-2)

3) Synthesis of a deprotected derivative of N-acetylglucosaminyldexamethasone

34 → 35β

[0075] A protected derivative of N-acetylglucosaminyldexamethasone 34 [56.0 mg (77.6 μmol)] was suspended in methanol (1 ml), and to this suspension was added 1 M sodium methoxide (16 μl) at room temperature. The mixture was stirred at room temperature for 50 min. The reaction solution which turned yellow was applied to a gel filtration column of LH-20, and eluted with methanol. Evaporation of the solvent was distilled off from fractions containing product *in vacuo* to give 35β as white powder [46.6 mg (yield 100%)].

Compound 35β

[0076]

$C_{30}H_{42}FNO_{10}$ MW = 595.66
MP : 208 - 211°C (decomp.)
FAB(+)MS 596 $(M+H)^+$, 618 $(M+Na)^+$

IR ν^{KBr} cm^{-1} : 3420(OH), 1718, 1660(C=O),
1620 (C=C)

^{1}H-NMR [500 MHz, CD_3CN, Ref = 1.950ppm(CH_3CN)]

δ ; 0.832 (3H, d, J = 7.3 Hz, 16-CH_3)
0.949 (3H, s, CH_3)

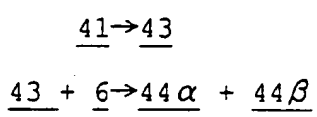
1.530 (3H, s, CH_3)
3.214 - 3.270 (2H, m, H-4_{GlcNAc}+ H-5 $_{GlcNAc}$)
3.400 (1H, dd, J = 8.1, 9.9 Hz, H-3 $_{GlcNAc}$)
3.548 (1H, dd, J = 8.4, 9.9 Hz, H-2 $_{GlcNAc}$)
3.596 (1H, dd, J = 6.2, 12.1 Hz, H-6 $_{GlcNAc}$)
3.816 (1H, dd, J = 1.5, 12.1 Hz, H' - 6 $_{GlcNAc}$)
4.383 (1H, d, J = 8.4 Hz, H-1 $_{GlcNAc}$)
6.029 (1H, s, H-4)
6.239 (1H, dd, J = 1.8, 10.3 Hz, H-1)
7.284 (1H, d, J = 10.3Hz, H-2)

Example 6

Synthesis of N-acetylgalactosaminyldexamethasone (Fig. 6)

1) Synthesis of a protected derivative of N-acetylgalactosaminyldexamethasone

[0077]



[0078] N-Acetylgalactosamine 41 [3.0 g (13.56 mmol)] was suspended in acetyl chloride (6 ml), and stirred at room temperature overnight. The reaction mixture was diluted with chloroform (24 ml), poured into ice-water, and the chloroform layer was washed with saturated sodium bicarbonate. The organic layer dried over anhydrous magnesium sulfate, and the solvent was evaporated *in vacuo* to give an N-acetylgalactosamine chloride 43 (4.35 g). To a mixture of dexamethasone 6 [5.95 g (15.17 mmol)], the N-acetylgalactosamine chloride 43 [5.55 g (15.17 mmol)], trityl chloride [4.23 g (15.17 mmol)] and zinc chloride [2.07 g (15.17 mmol)] was added nitromethane (130 ml), and the resulting mixture was stirred under an argon atmosphere at room temperature overnight. The reaction solution was diluted with chloroform, and filtered to remove insoluble materials. The filtrate was washed successively with saturated solutions of sodium bicarbonate and sodium chloride. After drying the organic layer over anhydrous magnesium sulfate, the solvent was distilled off *in vacuo*, and the residue thus obtained was purified by silica gel column chromatography (acetone:toluene = 2:3) to give fractions containing the desired product (950.8 mg). This fraction was further purified by HPLC using a reversed phase partition column (acetonitrile-water) to give α-anomer 44α [98.0 mg (yield 0.9%)] and β-anomer 44β [569.5 mg (yield 5.2%)], respectively, both as white powder.

Compound 44α

[0079]

$C_{36}H_{48}FNO_{14}$ MW = 721.77
MP : 165 - 167°C
FAB(+)MS ; 722$(M+H)^+$
IR ν_{max}^{KBr} cm^{-1} : 3440(O-H), 1755($COCH_3$), 1669(C=O), 1620(C=C)
^{1}H-NMR [500 MHz, $CDCl_3$, Ref = 0.000ppm(TMS)]

δ ; 0.917(3H, d, $J_{16CH3,16}$ = 7.3, 16-CH_3)
1.014(3H, s, H-18)
1.565(3H, s, H-19)
1.997, 2.008, 2.092, 2.196(3H x 4, each s, $COCH_3$ x 4)
3.918(1H, dd, $J_{6',6}$ = 11.0, $J_{6',5}$ = 8.8, H-$6'_{GalNAc}$)
4.066(1H, dd, $J_{5,6}$ = 5.1, H-5_{GalNAc})
4.350(1H, dd, H-6_{GalNAc})
4.498(1H, d, J_{gem} = 18.7, H-21')

4.547(1H, d, H-21)
4.623(1H, ddd, $J_{2,1}$ = 3.7, $J_{2,NH}$ = 9.9, $J_{2,3}$ = 11.4, H-2_{GalNAc})
4.849(1H, d, H-1_{GalNAc})
5.256(1H, dd, $J_{3,4}$ = 2.9, H-3_{GalNAc})
5.383(1H, d, H-4_{GalNAc})
6.113(1H, d, $J_{4,1}$ = 2.2, H-4)
6.325(1H, dd, $J_{1,2}$ = 9.9, H-1)
6.480(1H, d, NHAc)
7.235(1H, d, H-2)

Compound 44β

[0080]

$C_{36}H_{48}FNO_{14}$ MW = 721.77
MP : 174 - 177°C (decomp.)
FAB(+)MS ; 722$(M+H)^+$, 744$(M+Na)^+$

IR ν_{max}^{KBr} cm^{-1} : 3450(O-H), 1750($COCH_3$), 1660(C=O position-3), 1622 and 1604(C=C)

^{1}H-NMR [500 MHz, $CDCl_3$, Ref = 0.000ppm(TMS)]

δ ; 0.903(3H, d, $J_{16CH3,16}$ = 7.3, 16-CH_3)
0.993(3H, s, H-18)
1.564(3H, s, H-19)
2.000, 2.012, 2.090, 2.186 (3H x 4, each s, $COCH_3$ x 4)
3.850(1H, dd, $J_{5,6}$ = 5.9, $J_{5,6'}$ = 7.0, H-5_{GalNAc})
3.978(1H, dd, $J_{6',6}$ = 11.0, H-$6'_{GalNAc}$)
4.108(1H, ddd, $J_{2,1}$ = 8.4, $J_{2,NH}$ = 8.8, $J_{2,3}$ = 11.0, H-2_{GalNAc})
4.383(1H, dd, H-6_{GalNAc})
4.630(1H, d, J_{gem} = 18.3, H-21')
4.677(1H, d, H-1_{GalNAc})
4.682(1H, d, H-21)
5.174(1H, dd, $J_{3,4}$ = 3.3, H-3_{GalNAc})
5.338(1H, d, H-4_{GalNAc})
6.070(1H, d, NHAc)
6.112(1H, d, $J_{4,1}$ = 1.8, H-4)
6.328(1H, dd, $J_{1,2}$ = 9.9, H-1)
7.235(1H, d, H-2)

2) Synthesis of a deprotected derivative of N-acetylgalactosaminyldexamethasone (α)

44α→45α

[0081] A protected derivative of N-acetylgalactosaminyldexamethasone (α-anomer) 44α [70.0 mg (0.097 mmol)] was dissolved in methanol (3 ml), and to this solution was added 1 M CH_3ONa/MeOH (0.1 ml). The mixture was stirred at room temperature for 3 h. The reaction solution was applied to a gel filtration column of LH-20, eluted with methanol, and the solvent of fractions containing product was evaporated *in vacuo* to give 45α as white powder [54.9 mg (yield 95.0%)].

Compound 45α

[0082]

$C_{30}H_{42}FNO_{10}$ MW = 595.66
MP : 189 - 191°C
FAB(+)MS ; 596$(M+H)^+$, 618$(M+Na)^+$

IR ν_{max}^{KBr} cm^{-1} : 3426(O-H, 1715(C=O 20-position), 1665(C=O 3-position), 1620 and 1605(C=C)
^{1}H-NMR [500 MHz, CD_3OD, Ref = 0.000ppm(TMS)]

δ ; 0.864(3H, d, $J_{16CH3,16}$ = 7.3, 16-CH_3)
1.008(3H, s, H-18)
1.583(3H, s, H-19)
2.018(3H, s, $COCH_3$)
3.692 - 3.721 (1H, m, H-6'$_{GalNAc}$)
3.748 - 3.778 (2H, m, H-5$_{GalNAc}$, H-6$_{GalNAc}$)
3.819(1H, dd, $J_{3,2}$ = 11.0, $J_{3,4}$ = 2.9, H-3$_{GalNAc}$)
3.888(1H, d, H-4$_{GalNAc}$)
4.316(1H, dd, $H_{2,1}$ = 3.7, H-2$_{GalNAc}$)
4.527(1H, d, J_{gem} = 18.7, H-21')
4.580(1H, d, H-21)
4.801(1H, d, H-1$_{GalNAc}$)
6.076(1H, d, $J_{4,1}$ = 1.8, H-4)
6.283(1H, dd, $J_{1,2}$ = 10.3, H-1)
7.395(1H, d, H-2)

3) Synthesis of a deprotected derivative of N-acetylgalactosaminyldexamethasone (β)

<u>44β</u>→<u>45β</u>

[0083] A protected derivative of N-aceylgalactosaminyldexamethasone (β) <u>44β</u> [84.5 mg (0.117 mmol)] was dissolved in methanol (0.5 ml), and to this solution was added 1 M CH_3ONa/MeOH (24 μl), and the mixture was stirred at room temperature for 3 h. The reaction solution was applied to a gel filtration column, eluted with methanol, and the solvent of fractions containing product was evaporated *in vacuo* to give <u>45β</u> [63.9 mg (yield 91.7%)] as white powder.

Compound <u>45β</u>

[0084]

$C_{30}H_{42}FNO_{10}$ MW = 595.66
MP : 201 - 203°C
FAB(+)MS ; 596$(M+H)^+$, 618$(M+Na)^+$
IR ν_{max}^{KBr} cm^{-1} : 3420(O-H), 1720(C=O position-20), 1660(C=O position-3), 1620 and 1602(C=C)
^{1}H-NMR [500 MHz, CD_3OD, Ref = 3.300ppm(CH_3OD)]

δ ; 0.845(3H, d, $J_{16CH3,16}$ = 7.3, 16-CH_3)
0.986(3H, s, H-18)
1.575(3H, s, H-19)
2.018(3H, s, $COCH_3$)
3.472(1H, dd, $J_{5,6}$ = 7.3, $J_{5,6'}$ = 4.8, H-5$_{GalNAc}$)
3.636(1H, dd, $J_{3,2}$ = 10.6, $J_{3,4}$ = 2.9, H-3$_{GalNAc}$)
3.726(1H, dd, $J_{6',6}$ = 11.4, H-6'$_{GalNAc}$)
3.797(1H, d, H-4$_{GalNAc}$)
3.806(1H, dd, H-6$_{GalNAc}$)
3.912(1H, dd, $J_{2,1}$ = 8.4, H-2$_{GalNAc}$)
4.441(1H, d, H-1$_{GalNAc}$)
4.593(1H, d, J_{gem} = 18.3, H-21')
4.702(1H, d, H-21)
6.069(1H, d, $J_{4,1}$ = 1.8, H-4)
6.277(1H, dd, $J_{1,2}$ = 10.3, H-1)
7.396(1H, d, H-2)

4) N-Acetylgalactosaminyldexamethasone (modified method)

<u>43</u> + <u>6</u> → <u>44β</u> + <u>44'</u>

[0085] An N-acetylgalactosamine chloride (43) (2.8 g) and dexamethasone (6) [1.00 g (2.55 mmol)] were suspended in α-methylstyrene, and stirred at 70°C for 4.5 h. The reaction solution was diluted with chloroform, filtered to remove insoluble materials, and the solvent of the filtrate was evaporated *in vacuo*. The residue thus obtained was purified by silica gel column chromatography (chloroform:methanol = 20:1) to give fractions containing β-anomer (281.0 mg) and those containing oxazoline derivative (365.3 mg), respectively. The β-anomer containing fraction was further purified by silica gel column chromatography (ethyl acetate) to obtain pale yellow powder 44β [157.7 mg (yield 8.6%)], which was recrystallized from ethyl acetate (1 ml) to yield white powder (153.8 mg). The oxazoline derivative containing fraction was similarly purified by silica gel chromatography (ethyl acetate) to give an oxazoline derivative (44') as white powder [184.8 mg (yield 10.0%)].

Compound 44' (oxazoline derivative)

[0086]

$C_{36}H_{48}FNO_{14}$ MW = 721.77
MP : 213 - 215°C (decomp.)
FAB(+)MS ; 722$(M+H)^+$, 744 $(M+Na)^+$

IRv_{max}^{KBr} cm^{-1} : 3400(O-H), 1750($COCH_3$), 1722(C=O position-20), 1660(C=O position-3), 1618 and 1602(C=C)

^{1}H-NMR [500MHz, $CDCl_3$, Ref = 0.000ppm(TMS)]

δ ; 0.917(3H, d, $J_{16CH3,16}$ = 7.0, 16-CH_3)
1.080(3H, s, H-18)
1.562(3H, s, H-19)
2.019, 2.089, 2.123, 2.149 (3H x 4, each s, $COCH_3$ x 4)
4.225(1H, dd, $J_{6',6}$ = 11.4, $J_{6',5}$ = 6.6, H-6'$_{GalNAc}$)
4.250(1H, dd, $J_{6',5}$ = 4.4, H-6$_{GalNAc}$)
4.312(1H, ddd, $J_{2,1}$ = 1.1, $J_{2,NH}$ = 6.6, $J_{2,3}$ = 3.7, H-2$_{GalNAc}$)
4.418(1H, dd, $J_{4,3}$ = 6.2, $J_{4,5}$ = 3.7, H-4$_{GalNAc}$)
4.427(1H, d, J_{gem} = 17.2, H-21')
4.515(1H, d, H-21)
4.787(1H, dd, H-3$_{GalNAc}$)
5.064(1H, d, H-1$_{GalNAc}$)
5.424 - 5.454 (1H, m, H-5$_{GalNAc}$)
6.111(1H, d, $J_{4,1}$ = 1.8, H-4)
6.159(1H, d, NHAc)
6.333(1H, dd, $J_{1,2}$ = 10.3, H-1)
7.261(1H, d, H-2)

5) Synthesis of a deprotected oxazoline derivative of N-acetylgalactosaminyldexamethasone

44' →45'

[0087] A protected oxazoline derivative of N-acetylgalactosaminyldexamethasone (44') [89.0 mg (0.123 mmol)] was dissolved in methanol (1 ml), and to this solution was added 1 M CH_3ONa/MeOH (25 μl). The resulting mixture was stirred at room temperature for 2 h. The reaction solution was applied to a gel filtration column of LH-20, and eluted with methanol. The solvent of fractions containing product were evaporated *in vacuo* to give 45' as white powder [67.9 mg (yield 92.7%)].

Compound 45' (oxazoline derivative)

[0088]

$C_{30}H_{42}FNO_{10}$ MW = 595.66
MP : 169 - 172°C
FAB(+)MS ; 596$(M+H)^+$, 618$(M+Na)^+$

IR ν_{max}^{KBr} cm^{-1} : 3400(O-H), 1718(C=O position-20), 1660(C=O position-3), 1620 and 1602(C=C)
^{1}H-NMR [500MHz, CD_3OD, Ref = 3.300ppm(CH_3OD)]

δ : 0.853(3H, d, $J_{16CH3,16}$ =7.3, 16-CH_3)
1.006(3H, s, H-18)
1.579(3H, s, H-19)
1.960(3H, s, $COCH_3$)
3.601(2H, d, $J_{6,5}$ = 6.6, H-6_{GalNAc})
3.745(1H, dd, $J_{5,4}$ = 2.6, H-5_{GalNAc})
4.027(1H, d, $J_{4,3}$ = 5.9, H-4_{GalNAc})
4.058(1H, dd, $J_{3,2}$ = 3.7, H-3_{GalNAc})
4.228(1H, d, H-2_{GalNAc})
4.383(1H, d, J_{gem} = 18.3, H-21')
4.693(1H, d, H-21)
4.950(1H, s, H-1_{GalNAc})
6.070(1H, d, $J_{4,1}$ = 1.8, H-4)
6.278(1H, dd, $J_{1,2}$ = 9.9, H-1)
7.400(1H, d, H-2)

Example 7

Synthesis of β-glucuronyldexamethasone and toluoyl-protected derivative of β-glucuronyldexamethasone (Fig. 7)

1. Synthesis of β-glucuronyldexamethasone

[0089] 1) D-Glucuronolactone 51 (6.30 g) was suspended in methanol (100 ml), and to this suspension was added sodium hydroxide (12.6 mg). The compounds were completely solubilized by ultrasonic ation. After the solvent was distilled off from the mixture *in vacuo*, pyridine (6.0 ml) and acetic anhydride (12.0 ml) were added to the residue under ice-cooling. While the reaction temperature was slowly raised to room temperature, the resulting mixture was continuously stirred for 12 h. Under ice-cooling, methanol was added to the reaction mixture to precipitate 52 as white powder, which was collected by filtration [5.69 g (yield 42.3%)].

51		52
$C_6H_8O_6$ = 176.13	→	$C_{15}H_{20}O_{11}$ = 376.14

Compound 52

[0090]

MW : $C_{15}H_{20}O_{11}$ = 376.14
MP : 182 - 183°C
FD-MS : m/z = 376 $(M)^+$

IR ν^{KBr} cm^{-1} : 1763(C=O), 1374(CH_3),
1231, 1208(C-C(=O)-O)

^{1}H-NMR (ppm, 500 MHz, $CDCl_3$, Ref = 0.000ppm(TMS))

1 5.770 (1H, d, $J_{1,2}$ = 7.70Hz)
2 5.146 (1H, dd, $J_{2,1}$ = 7.70, $J_{2,3}$ = 9.16)
3 5.311 (1H, t, $J_{3,2}$ = $J_{3,4}$ = 9.16)
4 5.250 (1H, t, $J_{4,3}$ = 9.16, $J_{4,5}$ = 9.52)
5 4.181 (1H, d, $J_{5,4}$ = 9.52)

-COOC$\underline{H_3}$ 3.747 (3H, s)
-COC$\underline{H_3}$ 2.118, 2.031 (3H, s) x 2
-COC$\underline{H_3}$ 2.039 (6H, s)

2) 52 (2.26 g) was dissolved in dichloromethane (20 ml) was added, and to this solution, under ice-cooling, a hydrobromide-acetic acid solution (10.0 ml). The mixture was stirred at room temperature for 12 h. After the reaction solution was washed with saturated sodium bicarbonate solution, the organic layer was dried over anhydrous magnesium sulfate, and the solvent was evaporated *in vacuo*. The residue thus obtained was purified by silica gel column chromatography (toluene:ethyl acetate = 4:1) to give 53 as white powder [1.57 g (yield 65.8%)].

52 → 53

Compound 53

[0091]

MW : $C_{13}H_{17}O_9Br$ = 397.17
MP : 111 - 113°C
FAB(+)MS : m/z = 397, 399 $(M+H)^+$,

IR ν^{KBr} cm^{-1} : 1767, 1750(C=O), 1379(CH_3), 1252, 1229, 1215(C-C(=O)-O)

^{1}H-NMR (ppm, 500 MHz, $CDCl_3$, Ref = 0.000ppm(TMS))

1	6.643 (1H, d, $J_{1,2}$ = 4.03Hz)
2	4.859 (1H, dd, $J_{2,1}$ = 4.03, $J_{2,3}$ = 9.89)
3	5.616 (1H, t, $J_{3,2}$ = 9.89, $J_{3,4}$ = 9.52)
4	5.246 (1H, dd, $J_{4,3}$ = 9.52, $J_{4,5}$ = 10.62)
5	4.584 (1H, d, $J_{5,4}$ = 10.62)
-COOC$\underline{H_3}$	3.766 (3H, s)
-COC$\underline{H_3}$	2.100, 2.056, 2.052 (3H, s) x 3

[0092] 3) Dexamethasone 6 (1.54 g) was suspended in chloroform (150 ml), and to this solution were added, under an argon atomosphere, molecular shieve 4A (1.50 g) and silver carbonate (1.60 g) and 53 (1.53 g). The resulting mixture was stirred at room temperature for 4 days. After the reaction solution was filtered, the solvent of the filtrate was evaporated *in vacuo* to give crude 54' (2.80 g). Purification of the crude 54' (580 mg) by silica gel column chromatography (toluene:ethyl acetate = 2:1 → 1:1) gave 54' as white powder [220.6 mg (yield 38.0%)].

53 + 6 → 54'

Compound 54'

[0093]

MW $C_{35}H_{45}O_{14}F$ = 708.73
MP : 133 - 135°C
FAB(+)MS : m/z = 709 $(M+H)^+$, 731 $(M+Na)^+$

IRν^{KBr} cm^{-1} : 3396(O-H), 2944 (C-H), 1757, 1665(C=O), 1222(C-C(=O)-O)

^{1}H-NMR (ppm, 500 MHz, $CDCl_3$, Ref = 0.000ppm(TMS))

1	5.863 (1H, d, $J_{1,2}$ = 5.13Hz)
2	4.253 (1H, dd, $J_{2,1}$ = 5.13, $J_{2,3}$ = 2.57)
3	5.154 (1H, dd, $J_{3,2}$ = $J_{3,4}$ = 2.57)

4	5.191 (1H, dd, $J_{4,3}$ = 2.57, $J_{4,5}$ = 8.42)
5	4.256 (1H, d, $J_{5,4}$ = 8.42)
-COOC$\underline{H}_3$	3.788 (3H, s)
-COC$\underline{H}_3$	2.129, 2.121 (3H, s) x 2
C$\underline{H}_3$ (ortho ester)	1.754 (3H, s)

[0094] 4) 54' (441.4 mg) was dissolved in acetonitrile/water mixture [140 ml(4/96, containing 0.1% TFA)] , and this solution was applied in 20 ml portions to a HPLC column [μ-Bondasphere C_{18}-100 Å, flow-rate 23.0 ml/min, detection wave length 254 nm (UV), eluent A/B = water/95% acetonitrile (both containing 0.1% TFA) = 94/6 → 80/20 → 38/62], and eluted with the gradient for 30 min). Fractions containing product were evaporated *in vacuo*, and then lyophilized to give 54β as white powder [41.4 mg (yield 9.40%)].

54' → 54β

Compound 54β

[0095]

MW : $C_{35}H_{45}O_{14}F$ = 708.73
MP : 140 - 142°C
FAB(+)MS : m/z = 709 $(M+H)^+$, 731 $(M+Na)^+$

IR ν^{KBr} cm^{-1} : 3414(O-H), 2946 (C-H), 1759, 1664(C=O), 1222(C-C(=O)-O)

^{1}H-NMR (ppm, 500 MHz, $CDCl_3$, Ref = 0.000ppm(TMS))

1	4.844 (1H, d, $J_{1,2}$ = 7.70Hz)
2	5.066 (1H, dd, $J_{2,1}$ = 7.70, $J_{2,3}$ = 9.52)
3	5.293 (1H, t, $J_{3,2}$ = $J_{3,4}$ = 9.52)
4	5.213 (1H, t, $J_{4,3}$ = $J_{4,5}$ = 9.52)
5	4.037 (1H, d, $J_{5,4}$ = 9.52)
-COOC$\underline{H}_3$	3.767 (3H, s)
-COC$\underline{H}_3$	2.092, 2.038, 2.027 (3H, s) x 3

[0096] 5) 54' (823.1 mg) was dissolved in methanol (10 ml), and to this solution was added 1 M sodium methoxide (0.3 ml) at 0°C. The mixture was stirred at room temperature for 3 h. To this mixture were further added water (1 ml) and 1 M sodium methoxide (0.3 ml), and the resulting mixture was stirred at room temperature for 2 h. After the solvent of the reaction solution was evaporated *in vacuo*, water (10 ml) was added to the residue, and the mixture was filtered. The filtrate was lyophilized to give crude 55β (580.0 mg). This crude product was purified by HPLC under similar conditions as in 4). Fractions containing the product were evaporated *in vacuo*, and then lyophilized to give 55β as white powder [54.5 mg (yield 8.2%)].

54' → 55β

Compound 55β

[0097]

MW : $C_{28}H_{37}O_{11}F$ = 568.59
MP : 188 - 190°C
FAB(+)MS : m/z = 569 $(M+H)^+$, 591 $(M+Na)^+$

IR ν^{KBr} cm^{-1} : 3410(O-H), 2938 (C-H), 1716, 1662(C=O), 1607(C-C)

^{1}H-NMR ppm, 500 MHz (CD_3OD, Ref = 3.300ppm(CH_3OD))

1 4.523 (1H, d, $J_{1,2}$ = 7.74Hz)
2 3.482 (1H, dd, $J_{2,1}$ = 7.74, $J_{2,3}$ = 9.29)
3 3.554 (1H, t, $J_{3,2}$ = $J_{3,4}$ = 9.29)
4 3.702 (1H, t, $J_{4,3}$ = 9.29, $J_{4,5}$ = 9.51)
5 3.954 (1H, d, $J_{5,4}$ = 9.73)

2. Synthesis of a toluoyl-protected derivative of β-glucuronyldexamethasone (toluoyl derivative)

[0098] 1) D-Glucuronolactone 51 (4.86 g) was suspended in methanol (100 ml), and to this suspension was added sodium hydroxide (9.8 mg). The compounds were completely solublized by ultrasonic ation. After the solvent of the reaction solution was evaporated *in vacuo*, pyridine (50 ml), *p*-toluoyl chloride and chloroform (20 ml) were added to the residue under ice-cooling, and, while the reaction temperature was slowly raised to room temperatue, the mixture was stirred for 12 h. Water was added to the reaction mixture under ice-cooling, and the chloroform layer was washed successively with water, and saturated solutions of sodium bicarbonate and copper sulfate. After the chloroform solution was dried over anhydrous magnesium sulfate, the solvent was distilled off *in vacuo*. The residue thus obtained was purified by silica gel column chromatography (toluene:ethyl acetate = 30/1 → 20/1) to give white powder [14.7 g (yield 78.2%)] consisting of 57α and 57β in a ratio of 1:1.5.

51 → 57

Compound 57

[0099]

57α MW : $C_{39}H_{36}O_{11}$ = 680.706
MP : 83 - 85°C
FAB(-)MS : m/z = 679 $(M-H)^+$

IRν^{KBr} cm^{-1} : 1736, 1613(C=O)
1265(C-C(=O)-O)
1100(O-C-C)

^{1}H-NMR (ppm, 500 MHz, $CDCl_3$, Ref = 0.000ppm(TMS))

1 6.874 (1H, d, $J_{1,2}$ = 3.66Hz)
2 5.654 (1H, dd, $J_{2,1}$ = 3.66, $J_{2,3}$ = 9.89)
3 6.280 (1H, t, $J_{3,2}$ = $J_{3,4}$ = 9.89)
4 5.721 (1H, t, $J_{4,3}$ = $J_{4,5}$ = 9.89)
5 4.727 (1H, d, $J_{5,4}$ = 9.89)
-COOC$\underline{H}_3$ 3.669 (3H, s)
-$C_6H_4C\underline{H}_3$ 2.461, 2.372, 2.310, 2.304 (3H, s) x 4
-$C_6\underline{H}_4CH_3$ 8.028, 7.866, 7.792, 7.754, 7.327, 7.191, 7.118, 7.084 (2H, d, J = 8.06) x 8

57β MW : $C_{39}H_{36}O_{11}$ = 680.706
MP : 92 - 95°C
FAB(-)MS : m/z = 679 $(M-H)^+$

IR ν^{KBr} cm^{-1} : 1734, 1613(C=O)
1266(C-C(=O)-O)
1094(O-C-C)

^{1}H-NMR (ppm, 500 MHz, $CDCl_3$, Ref = 0.000ppm(TMS))

1 6.627 (1H, d, $J_{1,2}$ = 7.33Hz)
2 5.794 (1H, dd, $J_{2,1}$ = 7.33, $J_{2,3}$ = 8.79)
3 5.970 (1H, t, $J_{3,2}$ = $J_{3,4}$ = 8.79)

4	5.767 (1H, t, $J_{4,3} = J_{4,5} = 8.79$)
5	4.568 (1H, d, $J_{5,4} = 8.79$)
-COOC$\underline{H}_3$	3.606 (3H, s)
-$C_6H_4C\underline{H}_3$	2.377, 2.326 (6H, s) x 4
-$C_6\underline{H}_4CH_3$	7.909, 7.850, 7.127, 7.116 (2H, d, J = 8.06) x 4 7.797, 7.185 (4H, d, J = 8.06) x 2

[0100] 2) 57 (6.22 g) was dissolved in dichloromethane (100 ml), and to this solution was added, under ice-cooling, a hydrobromide-acetic acid solution (40 ml). The mixture was stirred at room temperature for 12 h. After the reaction solution was washed with saturated sodium bicarbonate solution, the organic layer was dried over anhydrous magnesium sulfate. The solvent was evaporated *in vacuo* to give 58 as white powder [5.54 g (yield 96.3%)].

57 → 58

Compound 58

[0101]

MW : $C_{31}H_{29}O_9Br$ = 625.468
MP : 83 - 84°C
FAB(+)MS : m/z = 625, 627 $(M+H)^+$

IRv^{KBr} cm^{-1} : 1733, 1613(C=O)
1266(C-C(=O)-O)
1106(O-C-C)

^{1}H-NMR (ppm, 500 MHz, $CDCl_3$, Ref = 0.000ppm(TMS))

1	6.884 (1H, d, $J_{1,2} = 4.03$Hz)
2	5.308 (1H, dd, $J_{2,1} = 4.03$, $J_{2,3} = 9.89$)
3	6.241 (1H, t, $J_{3,2} = J_{3,4} = 9.89$)
4	5.692 (1H, t, $J_{4,3} = J_{4,5} = 9.89$)
5	4.835 (1H, d, $J_{5,4} = 9.89$)
-COOC$\underline{H}_3$	3.677 (3H, s)
-$C_6H_4C\underline{H}_3$	2.370, 2.358, 2.299 (3H, s) x 3
-$C_6\underline{H}_4CH_3$	7.872, 7.864, 7.784, 7.196, 7.186, 7.107 (2H, d, J = 8.06) x 6

[0102] 3) Dexamethasone 6 (0.94 g) was dissolved in dehydrated tetrahydrofuran (100 ml), and to this solution were added, under an argon atmosphere, molecular sieve 5A (1.0 g) and 58 (1.98 g). To the resulting mixture was added, under ice-cooling, a solution (0.6 ml) of silver triflate (1.27 g) and tetramethylurea in dehydrated tetrahydrofuran, and, while the reaction temperature was slowly raised to room temeperture, the resulting mixture was stirred for 1 h. After the reaction solution was filtered, the solvent was evaporated from the filtrate *in vacuo*, and the residue thus obtained was taken up in ethyl acetate (200 ml). After this solution was dried over anhydrous magnesium sulfate, the solvent was evaporated *in vacuo*. The residue thus obtained was purified by silica gel column chromatography (chloroform:methanol = 60/1) followed by HPLC (column μ-Bondasphere C_{18}-100 Å, flow rate 23.0 ml/min, detection wave length 254 nm (UV), eluent A/B = water/95% acetonitrile (both containing 0.1% TFA) = 30/70 → 0/100, eluted with the gradient 30 min). Fractions containing product were evaporated *in vacuo*, and then lyophilized to give 59α [50.0 mg (yield 2.2%)] and 59β [163.3 mg (yield 7.3%)], both as white powder.

58 + 6 → 59

Compound 59

[0103]

59α MW : $C_{53}H_{57}O_{14}F$ = 937.23
MP : 146 - 150°C
FAB(+)MS : m/z = 937 $(M+H)^+$, 919 $(M-OH)^+$

IRv^{KBr} cm^{-1} : 3414(O-H), 2948(C-H)
1732, 1660, 1613(C=O)
1267(C-C(=O)-O)
1106(O-C-C)

^{1}H-NMR (ppm, 500 MHz, $CDCl_3$, Ref = 0.000ppm(TMS))

1	5.465 (1H, d, $J_{1,2}$ = 4.03Hz)
2	5.287 (1H, dd, $J_{2,1}$ = 4.03, $J_{2,3}$ = 9.89)
3	6.245 (1H, t, $J_{3,2} = J_{3,4}$ = 9.89)
4	5.370 (1H, t, $J_{4,3} = J_{4,5}$ = 9.89)
5	5.465 (1H, d, $J_{5,4}$ = 9.89)
-COOC$\underline{H}_3$	3.623 (3H, s)
-$C_6H_4C\underline{H}_3$	2.373, 2.355, 2.306 (3H, s) x 3
-$C_6\underline{H}_4CH_3$	7.862, 7.850, 7.784, 7.178, 7.165, 7.099 (2H, d, J = 8.06) x 6

59β MW : $C_{53}H_{57}O_{14}F$ = 937.23
MP : 155 - 160°C
FAB(+)MS : m/z = 937 $(M+H)^+$, 919 $(M-OH)^+$

IRv^{KBr} cm^{-1} : 3440(O-H), 2950(C-H)
1733, 1667, 1613(C=O)
1280, 1265(C-C(=O)-O)
1097(O-C-C)

^{1}H-NMR (ppm, 500 MHz, $CDCl_3$, Ref = 0.000ppm(TMS))

1	5.147 (1H, d, $J_{1,2}$ = 7.70Hz)
2	5.533 (1H, dd, $J_{2,1}$ = 7.70, $J_{2,3}$ = 9.16)
3	5.911 (1H, t, $J_{3,2}$ = 9.16, $J_{3,4}$ = 9.52)
4	5.598 (1H, t, $J_{4,3} = J_{4,5}$ = 9.52)
5	4.317 (1H, d, $J_{5,4}$ = 9.52)
-COOC$\underline{H}_3$	3.644 (3H, S)
-$C_6H_4C\underline{H}_3$	2.373, 2.359, 2.308 (3H, S) x 3
-$C_6\underline{H}_4CH_3$	7.857, 7.811, 7.768, 7.187, 7.171, 7.106 (2H, d, J = 8.06) x 6

Example 8

Synthesis of β-galacturonyldexamethasone and the toluoyl-protected derivative of β-galacturonyldexamethasone (Fig. 8)

1. Synthesis of β-galacturonyldexamethasone

[0104] 1) D-Galacturonic acid 61 (1.98 g) was dissolved in dehydrated methanol (100 ml), and to this solution was added a solution of diazomethane in ether in small portions under stirring until bubbling ceased. After the solvent was distilled off *in vacuo*, pyridine (4 ml) and acetic anhydride (8 ml) were added to the residue thus obtained under ice-cooling, and, while the reaction temperature was slowly raised to room temperature, the resulting mixture was stirred for 24 h. Then, after the addition of methanol under ice-cooling, the solvent was distilled off *in vacuo*. The residue was dissolved in chloroform, washed with copper sulfate solution, and then the chloroform layer was evaporated *in vacuo*. After the residue was dissolved in chloroform (4 ml), a hydrogenbromide-acetic acid solution (10.0 ml) was added under ice-cooling, and the resulting mixture was stirred for 3.5 h. Then, to this mixture was added hydrogenbromide-acetic acid solution (2.0 ml) under ice-cooling, and the resulting mixture was stirred for 1 h. After the reaction solution was evaporated *in vacuo*, the residue was dissolved in chloroform (80 ml), washed with saturated sodium bicarbonate solution, and dried over anhydrous magnesium sulfate. The solvent was distilled off *in vacuo*, and the residue thus obtained was purified by silica gel column chromaography (toluene:ethyl acetate = 4:1) to give 63 as white powder [1.17 g (yield 28.8%)].

61 → 63

Compound 63

[0105]

MW : $C_{13}H_{17}O_9Br$ = 397.17
MP : 131 - 134°C
FAB(+)MS : m/z =395, 397 $(M+H)^+$

IR ν^{KBr} cm^{-1} : 1769, 1748(C=O), 1375(CH_3)
1232, 1218(C-C(=O)-O)

^{1}H-NMR (ppm, 500 MHz, $CDCl_3$, Ref = 0.000ppm(TMS))

1	6.772 (1H, d, $J_{1,2}$ = 4.03Hz)
2	5.108 (1H, dd, $J_{2,1}$ = 4.03, $J_{2,3}$ = 10.62)
3	5.456 (1H, dd, $J_{3,2}$ = 10.62, $J_{3,4}$ = 3.30)
4	5.833 (1H, dd, $J_{4,3}$ = 3.30, $J_{4,5}$ = 1.1)
5	4.879 (1H, d, $J_{5,4}$ = 1.1)
-COOCH_3	3.777 (3H, s)
-COCH_3	2.111 (3H, s)
-COCH_3	2.024 (6H, s)

[0106] 2) Dexamethasone 6 (0.82 g) was dissolved in chloroform (100 ml), and to this solution were added, under an argon atmosphere, molecular sieve 4A (1.57 g), silver carbonate (1.62 g) and 63 (1.02 g). The resulting mixture was stirred at room temperature for 2 days. After the reaction solution was filtered, the filtrate was washed with saturated sodium chloride solution, and dried over anhydrous magnesium sulfate. Evaporation of the solvent *in vacuo* gave crude 64' (1.86 g). Purification of crude 64' (0.16 g) by silica gel PLC plate (chloroform/methanol = 20/1) gave 64' [0.041 g (yield 26.0%)] as white powder.

63 + 6 → 64'

Compound 64'

[0107]

MW : $C_{35}H_{45}O_{14}F$ = 708.73
MP : 141 - 142°C
FAB(+)MS : m/z = 709 $(M+H)^+$

IR ν^{KBr} cm^{-1} : 3454(O-H)
2950(C-H)
1757, 1665(C=O)
1237(C-C(=O)-O)

^{1}H-NMR (ppm, 500 MHz, $CDCl_3$, Ref = 0.000ppm(TMS))

1	5.791 (1H, d, $J_{1,2}$ = 4.40Hz)
2	4.273 (1H, dd, $J_{2,1}$ = 4.40, $J_{2,3}$ = 5.86)
3	5.260 (1H, dd, $J_{3,2}$ = 5.86, $J_{3,4}$ = 2.93)
4	5.791 (1H, dd, $J_{4,3}$ = 2.93, $J_{4,5}$ = 4.39)
5	4.867 (1H, d, $J_{5,4}$ = 4.39)
-COOCH_3	3.753 (3H, s)
-COCH_3	2.091, 2.074 (3H, s)
-CH_3 (ortho ester)	1.660 (3H, s)

[0108] 3) 64' (277.4 mg) was dissolved in a mixture of acetonitrile/water [100 ml(4/96, containing 0.1% TFA)] , and this solution was applied in 20 ml-portions to HPLC column (μ -Bondasphere C_{18}-100 Å, flow rate 23.0 ml/min, detection wave length 254 nm (UV), eluent A/B = water/95% acetonitrile (both containing 0.1% TFA) = 94/6 → 80/20 →

38/62, eluted with the gradient for 30 min). Fractions containing product were evaporated *in vacuo*, and then lyophilized to give 64β as white powder [67.5 mg (yield 24.3%)].

64' → 64β

Compound 64β

[0109]

MW : $C_{35}H_{45}O_{14}F$ = 708.73
MP : 155 - 158°C
FAB(+)MS : m/z = 709 $(M+H)^+$, 731 $(M+Na)^+$

IR ν^{KBr} cm^{-1} : 3406(O-H), 1754, 1665(C=O)
1225(C-C(=O)-O)

^{1}H-NMR (ppm, 500 MHz, $CDCl_3$, Ref = 0.000ppm(TMS))

1	4.893 (1H, d, $J_{1,2}$ = 8.06Hz)
2	5.277 (1H, dd, $J_{2,1}$ = 8.06, $J_{2,3}$ = 10.26)
3	5.100 (1H, dd, $J_{3,2}$ = 10.26, $J_{3,4}$ = 3.29)
4	5.689 (1H, dd, $J_{4,3}$ = 3.29, $J_{4,5}$ = 1.46)
5	4.297 (1H, d, $J_{5,4}$ = 1.46)
-COOCH_3	3.764 (3H, s)
-COCH_3	2.144, 2.096, 2.001 (3H, s) x 3

[0110] 4) 64' (103.3 mg) was dissolved in methanol (5 ml), and to this solution was added 1 M sodium methoxide (0.5 ml) at 0°C. The resulting solution was stirred at room temperature for 3 h. After the reaction solution was evaporated *in vacuo*, 1 M sodium methoxide (0.5 ml) and water (1 ml) were added to the residue at 0°C, and stirred at room temperature for 2 h. The reaction solution was evaporated *in vacuo*, and then lyophilized, was purified by HPLC under similar conditions as in 3). Fractions containing the product were evaporated *in vacuo* and then lyophilized to give 65β [29.5 mg (yield 35.5%)] and 66 [31.3 mg (yield 39.0%)], both as white powder.

64' → 65β + 66

Compound 65β

[0111]

MW : $C_{28}H_{37}O_{11}F$ = 568.59
MP : 187 - 189°C
FAB(+)MS : m/z = 569 $(M+H)^+$, 591 $(M+Na)^+$

IR ν^{KBr} cm^{-1} : 3414(O-H), 1713, 1662(C=O)
1617, 1605(C-C)

^{1}H-NMR (ppm, 500 MHz, CD_3OD, Ref = 3.300ppm(CH_3OD))

1	4.134 (1H, d, $J_{1,2}$ = 7.70Hz)
2	3.617 (1H, dd, $J_{2,1}$ = 7.70, $J_{2,3}$ = 9.89)
3	3.558 (1H, dd, $J_{3,2}$ = 9.89, $J_{3,4}$ = 3.30)
4	4.157 (1H, dd, $J_{4,3}$ = 3.30, $J_{4,5}$ = 1.10)
5	4.217 (1H, d, $J_{5,4}$ = 1.10)

Compound 66

[0112]

MW : $C_{28}H_{35}O_{10}F$ = 550.58
MP : 183 - 184°C
FAB(+)MS : m/z = 551 $(M+H)^+$, 573 $(M+Na)^+$

IR ν^{KBr} cm^{-1}: 3414(O-H), 1713, 1662(C=O)
1617, 1605(C-C), 1242(C-C(=O)-O)

^{1}H-NMR (ppm, 500 MHz, CD_3OD, Ref = 3.300ppm(CH_3OD))

1	6.151 (1H, d, $J_{1,2}$ = 4.03Hz)
2	4.012 (1H, t, $J_{2,1} = J_{2,3}$ = 4.03)
3	3.868 (1H, t, $J_{3,2} = J_{3,4}$ = 4.03)
4	5.098 (1H, d, $J_{4,3}$ = 4.40)

2. Synthesis of toluoyl-protected derivative of β-galacturonyldexamethasone

[0113] 1) D-Galacturonic acid 61 (1.12 g) was dissolved in dehydrated methanol (30 ml), and to this solution was added, under stirring, diazomethane in ether in small portions until bubbling ceased. After removal of the solvent *in vacuo*, pyridine (5 ml), *p*-toluoyl chloride (5 ml) and chloroform (10 ml) were added to the residue under ice-cooling, and the resulting mixture was stirred for 4 h, while the reaction temperature was slowly raised to room temperature. Then, to the reaction mixture was added water under ice-cooling, and the chloroform layer was washed successively with water, saturated solutions of sodium bicarbonate and copper sulfate. After the solution was dried over anhydrous magnesium sulfate, the solvent was distilled off *in vacuo*. Purification of the residue thus obtained by silica gel column chromatography (toluene:ethyl acetate = 40/1 → 30/1) gave 67 as white powder [782.7 mg (yield 20.2%)].

61 → 67

Compound 67β

[0114]

MW : $C_{39}H_{36}O_{11}$ = 680.706
MP : 180 - 182°C
FAB(-)MS : m/z = 679 $(M-H)^+$

IRν^{KBr} cm^{-1} : 1771, 1733, 1613(C = O)
1267(C-C(=O)-O)
1093(O-C-C)

^{1}H-NMR(ppm, 500MHz, $CDCl_3$, Ref = 0.000ppm(TMS))

1	6.215 (1H, d, $J_{1,2}$ = 8.06Hz)
2	6.065 (1H, dd, $J_{2,1}$ = 8.06, $J_{2,3}$ = 10.26)
3	5.733 (1H, dd, $J_{3,2}$ = 10.26, $J_{3,4}$ = 3.30)
4	6.207 (1H)
5	4.809 (1H, d, $J_{5,4}$ = 1.47)
-COOCH_3	3.700 (3H, s)
-C_6H_4CH_3	2.434, 2.378, 2.310, 2.296 (3H, s) x 4
-$C_6H_4$$CH_3$	7.953, 7.951, 7.769, 7.710, 7.266, 7.205, 7.101, 7.072 (2H, d, J = 8.06) x 8

[0115] 2) 67 (70.3 mg) was dissolved in dichloromethane (5 ml), and to this solution was added, under ice-cooling, a hydrogenbromide-acetic acid solution (2 ml). The mixture was stirred at room temperature for 2 h. The reaction solution was washed with saturated sodium bicarbonate solution, and then dried over anhydrous magnesium sulfate. Evaporation of the solvent *in vacuo* gave 68 [44.6 mg (yield 69.2%)] as white powder.

67 → 68

Compound 68

[0116]

MW : $C_{31}H_{29}O_9Br$ = 625.468
FAB(+)MS : m/z = 625, 627 $(M+H)^+$
^{1}H-NMR(ppm, 500MHz, $CDCl_3$, Ref = 0.000ppm(TMS))

1	7.003 (1H, d, $J_{1,2}$ = 4.03Hz)
2	5.612 (1H, dd, $J_{2,1}$ = 4.03, $J_{2,3}$ = 10.26)
3	6.006 (1H, dd, $J_{3,2}$ = 10.26, $J_{3,4}$ = 3.30)
4	6.255 (1H, dd, $J_{4,3}$ = 3.30, $J_{4,5}$ = 1.46)
5	5.132 (1H, d, $J_{5,4}$ = 1.46)
-COOCH_3	3.724 (3H, s)
-$C_6H_4CH_3$	2.429, 2.359, 2.316 (3H, s) x 3
-C_6H_4CH_3	7.895, 7.866, 7.695, 7.710, 7.254, 7.183, 7.073 (2H, d, J = 8.06) x 6

[0117] 3) Dexamethasone 6 (88.0 mg) was dissolved in dehydrated tetrahydrofuran (10 ml), and to this solution were added, under an argon atmosphere, molecular sieve 5A (1.0 g) and 68 (100.8 mg) dissolved in dehydrated tetrahydrofuran (10 ml). Then, to the resulting mixture were added, under ice-cooling, silver triflate (82.2 mg) dissolved in dehydrated tetrahydrofuran (2 ml) and tetramethylurea (0.25 ml), and, while the reaction temperature was slowly raised to room temperature, the resulting mixture was stirred for 2 h. The reaction solution was filtered, and the solvent of the filtrate was evaporated *in vacuo*. The residue thus obtained was dissolved in ethyl acetate (100 ml), washed with saturated sodium chloride solution. The solvent of the solution was evaporated *in vacuo*. The residue thus obtained was purified by HPLC (column: μ-Bondasphere C_{18}-100 Å, flow rate 23.0 ml/min, detection wave length 254 nm (UV), eluent A/B = water/95% acetonitrile (both containing 0.1% TFA) = 30/70 → 0/100, eluted with gradient for 30 min). Fractions containing product were evaporated *in vacuo*, and lyophilized to give 69α [9.5 mg (yield 4.6%)] and 69β [38.1 mg (yield 18.5%)], both as white powder.

68 + 6 → 69

Compound 69

69α

[0118]

MW : $C_{53}H_{57}O_{14}F$ = 937.023
MP : 161 - 167°C
FAB(+)MS : m/z = 937 $(M+H)^+$, 919 $(M-OH)^+$

IR ν^{KBr} cm^{-1}: 3414(O-H), 2928(C-H)
1731, 1667, 1612(C = O)
1283, 1267(C-C(=O)-O)
1095(O-C-C)

^{1}H-NMR(ppm, 500MHz, $CDCl_3$, Ref = 0.000ppm(TMS))

1	5.542 (1H, d, $J_{1,2}$ = 4.03Hz)
2	5.634 (1H, dd, $J_{2,1}$ = 4.03, $J_{2,3}$ = 10.63)
3	6.065 (1H, dd, $J_{3,2}$ = 10.63, $J_{3,4}$ = 3.30)
4	6.251 (1H, dd, $J_{4,3}$ = 3.30, $J_{4,5}$ = 1.46)
5	5.231 (1H, d, $J_{5,4}$ = 1.46)
-COOCH_3	3.678 (3H, s)
-$C_6H_4CH_3$	2.424, 2.347, 2.310 (3H, s) x 3
-C_6H_4CH_3	7.894, 7.858, 7.696, 7.244, 7.156, 7.061 (2H, d, J = 8.06) x 6

69β

[0119]

MW : $C_{53}H_{57}O_{14}F$ = 937.023
MP : 161 - 165°C
FAB(+)MS : 937 $(M+H)^+$, 919 $(M-OH)^+$

IR ν^{KBr} cm^{-1} : 3412(O-H), 2930(C-H)
1733, 1666, 1612(C = O)
1283, 1266(C-C(= O)-O),
1095(O-C-C)

^{1}H-NMR(ppm, 500MHz, $CDCl_3$, Ref = 0.000ppm(TMS))

1	5.151 (1H, d, $J_{1,2}$ = 8.42Hz)
2	5.904 (1H, dd, $J_{2,1}$ = 8.42, $J_{2,3}$ = 10.26)
3	5.632 (1H, dd, $J_{3,2}$ = 10.26, $J_{3,4}$ = 3.30)
4	6.029 (1H, dd, $J_{4,3}$ = 3.30, $J_{4,5}$ = 1.10)
5	5.565 (1H, d, $J_{5,4}$ = 1.10)
-COOCH_3	3.760 (3H, s)
-$C_6H_4CH_3$	2.373, 2.361, 2.299 (3H, s) x 4
-$C_6H_4CH_3$	7.975, 7.852, 7.706, 7.285, 7.178, 7.071 (3H, d, J = 8.06) x 6

Example 9

Synthesis of β-fucosyldexamethasone (Fig. 9)

1) Synthesis of SMe derivative of fucose (71 → 72 → 73α + 73β)

[0120] L-(-)Fucose 71 [3.0 g (18.27 mmol)] was suspended in acetic anhydride (30 ml), and to this solution was added, at 0°C, pyridine (7.1 ml) drop-wise. The mixture was stirred at room temperature overnight. The reaction solution was poured into ice-water, and extracted with chloroform four times. After the chloroform layer was washed successively with copper sulfate solution, water three times, and saturated sodium chloride solution. After the organic layer was dried over anhydrous magnesium sulfate, the solvent was distilled off *in vacuo*. The residue thus obtained was dissolved in ethyl acetate, and allowed to stand at -30°C for 2 days. Precipitated crystals were collected by filtration, weighing 2.98 g (yield 51.6%) of 72 as white powder. The product thus obtained [2.0 g (6.32 mmol)] and Bu_3SnSMe [3.20 g (9.48 mmol)] were dissolved in dichloroethane (20 ml), and to this solution was added at 0°C tin(IV) chloride [0.96 ml (8.22 mmol)] drop-wise. The mixture was stirred at room temperature overnight. The reaction solution was diluted with chloroform, and to this mixture was added potassium fluoride. After stirring, the mixture was filtered through celite. The chloroform layer of the filtrate was washed with saturated sodium bicarbonate, water and saturated sodium chloride solution, dried over anhydrous magnesium sulfate, and the solvent was distilled off *in vacuo*. Purification of the residue thus obtained by silica gel column chromatography (ethyl acetate:toluene = 1:6) gave α-anomer (73α) [164.2 mg (yield 8.1%)] and β-anomer (73β) [1.483 g (yield 73.2%)], both as white powder.

Compound 73α

[0121]

$C_{13}H_{20}O_7S$
MW : 320.36
MP : 78 - 80°C
FAB(+)MS : 321 $(M+H)^+$, 641 $(2M+H)^+$
IRν^{KBr} cm^{-1} : 1755, 1742(OCOCH$_3$)
^{1}H-NMR [500MHz, $CDCl_3$, Ref = 0.000ppm(TMS)]

δ; 1.169 (3H, d, J = 6.6Hz, H-6)
1.991, 2.053, 2.071, 2.170 (each 3H, 4s, SCH_3+3Ac)

4.449 (1H, q, J = 6.6Hz, H-5)
5.239 (1H, dd, J = 3.3, 10.6Hz, H-3)
5.291 (1H, dd, J = 5.5, 10.6Hz, H-2)
5.299 (1H, dd, J = 0.7, 3.3Hz, H-4)
5.568 (1H, d, J = 5.5Hz, H-1)

Compound 73β

[0122]

$C_{13}H_{20}O_7S$
MW : 320.36
MP : 146 - 147°C
FAB(+)MS : 321 $(M+H)^+$, 641 $(2M+H)^+$
IRν^{KBr} cm^{-1} : 1746($OCOCH_3$)
^{1}H-NMR [500MHz, $CDCl_3$, Ref = 0.000ppm(TMS)]

δ ; 1.224 (3H, d, J = 6.2Hz, CH_3-6)
1.990, 2.074, 2.178, 2.200 (each 3H, 4s, SCH_3+3Ac)
3.850 (1H, dq, J = 1.1, 6.2Hz, H-5)
4.361 (1H, d, J = 9.9Hz, H-1)
5.057 (1H, dd, J = 3.3, 9.9Hz, H-3)
5.248 (1H, t, J = 9.9Hz, H-2)
5.282 (1H, dd, J = 1.1, 3.3Hz, H-4)

2) Synthesis of a protected derivative of fucosyldexamethasone

[0123] To a mixture of dexamethasone (6) [51 mg (0.130 mmol)], β-anomer (73β) of fucose SMe-derivative [50 mg (0.156 mmol)] and molecular sieve 4A (100 mg) was added tetrahydrofuran (about 1 ml), and then, under an argon atmosphere at -20°C, methyl triflate (36 μl) was added. After stirring at room temperature for 2.5 h, the reaction mixture was neutralized with Et_3N, diluted with ethyl acetate, and filtered. The filtrate was washed successively with saturated solutions of sodium bicarbonate and sodium chloride. After the solution was dried over anhydrous magnesium sulfate, the solvent was evaporated *in vacuo*. Purification of the residue thus obtained by silica gel column chromatography (ethyl acetate:toluene = 1:1) gave α-anomer (74α) [6.5 mg (yield 7.5%)] and β-anomer (74β) [20.9 mg (yield 24.2%)], both as white powder.

73β + dexamethasone (6) → 74α + 74β

Compound 74α (fuc(OAc)dexa(α))

[0124]

$C_{34}H_{45}FO_{12}$ MW = 664.72
MP : 120 - 121°C
FAB(+)MS 665 $(M+H)^+$

IR ν^{KBr} cm^{-1} 3470(O-H)
1750(C=O of OAc)
1662(C=O at position-3)
1622, 1604(C = C)
1070, 1058(C-O of OH)

^{1}H-NMR(500MHz, $CDCl_3$, Ref = 0.000ppm(TMS))

δ : 0.896 (3H, d, J = 6.6Hz, 16-CH_3)
1.028 (3H, s, CH_3)
1.150 (3H, d, J = 6.6 Hz, H_3-6_{fuc})
1.543 (3H, s, CH_3)

2.000 (3H, s, Ac)
2.171 (6H, s, 2Ac)
4.253 (1H, q, J = 6.6Hz, H-5_{fuc})
4.386 (1H, d, J = 17.2Hz, H-21)
4.516 (1H, d, J = 17.2Hz, H'-21)
5.028 (1H, d, J = 3.7 Hz, H-1_{fuc})
5.171 (1H, dd, J = 3.7, 11.0Hz, H-2_{fuc})
5.310 (1H, dd, J = 1.1, 3.3 Hz, H-4_{fuc})
5.436 (1H, dd, J = 3.3, 11.0Hz, H-3_{fuc})
6.112 (1H, s, H-4)
6.331 (1H, dd, J = 1.8, 10.3Hz, H-1)
7.189 (1H, dd, J = 10.3Hz, H-2)

Compound 74β (fuc(OAc)dexa(β)

[0125]

$C_{34}H_{45}FO_{12}$ MW = 664.72
MP : 134 - 137°C
FAB(+)MS 665 $(M+H)^+$

IRv^{KBr} cm^{-1} 3494(O-H)
1754(OCOCH$_3$)
1666(C = O)
1623, 1604(C = C)
1075, 1035(C-O)

^{1}H-NMR(500MHz, $CDCl_3$, Ref = 0.000 ppm(TMS))

δ : 0.905 (3H, d, J = 7.3Hz, 16-CH_3)
0.993 (3H, s, CH_3)
1.220 [3H, d, J = 6.6Hz, H_3-6(fuc)]
1.549 (3H, s, CH_3)
1.998, 2.113, 2.167 (each 3H, 3s, 3OAc)
3.806 [1H, d, J = 0.7, 6.6Hz, H-5(fuc)]
4.484 (1H, d, J = 16.5Hz, H-21)
4.562 (1H, d, J = 16.5Hz, H'-21)
5.564 [1H, d, J = 7.7Hz, H-1(fuc)]
5.040 [1H, dd, J = 3.3, 10.6Hz, H-3(fuc)]
5.227 [1H, dd, J = 7.7, 10.6Hz, H-2(fuc)]
5.240 [1H, dd, J = 3.3, 0.7Hz, H-4(fuc)]
6.110 (1H, s, H-4)
6.325 (1H, dd, J = 2.2, 9.9Hz, H-1)
7.237 (1H, d, J = 9.9Hz, H-2)

3) Synthesis of deprotected derivative of fucosyldexamethasone (74β → 75β)

[0126] A protected derivative of fucosyldexamethasone (74β) [112.4 mg (0.169 mmol)] was dissolved in methanol (1 ml), and to this solution was added 1 M sodium methoxide (35 μl). The mixture was stirred at room temperature for 1 h. The reaction solution was applied to a gel filtration column of LH-20, and eluted with methanol. Evaporation of the solvent of fractions containing the product *in vacuo* gave 75β [79.4 mg (yield 87.2%)] as white powder.

Compound 75β

[0127]

$C_{28}H_{39}FO_9$ MW = 538.61
MP : 161 - 164°C

FAB(+)MS 539 $(M+H)^+$

IRv^{KBr} cm^{-1} 3418 (OH)
1717, 1665 (C=O), 1622, 1602 (C=C)

^{1}H-NMR (500MHz, CD_3OD, Ref = 3.350 ppm (CH_3OD)

δ : 0.906 (3H, d, J=7.3Hz, 16-CH_3)
1.054 (3H, s, CH_3)
1.318 (3H, d, J=6.6Hz, H_3-6_{fuc})
1.628 (3H, s, CH_3)
3.516 (1H, dd, J=3.3, 9.9Hz, H-3_{fuc})
3.604 (1H, dd, J=7.3, 9.9Hz, H-2_{fuc})
3.631 (1H, d, J=3.3Hz, H-4_{fuc})
3.682 (1H, q, J=6.6Hz, H-5_{fuc})
4.239 (1H, d, J=7.3Hz, H-1_{fuc})
4.683 (2H, s, H_2-21)
6.120 (1H, s, H-4)
6.329 (1H, dd, J=1.8, 10.3Hz, H-1)
7.445 (1H, d, J=10.3Hz, H-2)

Example 10

Synthesis of sodium salt of sialyldexamethasone (Fig. 10)

1) Synthesis of a protected derivative of sialyl dexamethasone

[0128] Methyl 2-chloro-4,7,8,9-tetra-O-acetyl-N-acetylneuraminate (81) was synthesized by the method described in Carbohy. Res. 158 (1986), 35-51.

[0129] Dexamethasone (6) [7.0 g (18.0 mmol)] was dissolved in tetrahydofuran (130 ml), and to this solution were added molecular sieve 4A (70 g) and methyl 2-chloro-4,7,8,9-tetra-O-acetyl-N-acetylneuraminate (81) [11.08 g (21.6 mmol)]. To this mixture was added, under an argon atmosphere, a solution of silver triflate [5.60 g (21.6 mmol)] in tetrahydrofuran at -40°C. While the reaction temperature was slowly raised to room temperature, the mixture was stirred for 1.5 h. To this mixture was further added 81 [4.63 g (9.0 mmol)], and the resulting mixture was stirred at room temperature overnight. After the reaction solution was filtered, the solvent of the filtrate was evaporated *in vacuo*. The residue was dissolved in ethyl acetate (200 ml), washed with saturated sodium chloride solution and dried over anhydrous magnesium sulfate. After the solvent was distilled off *in vacuo*, the residue thus obtained was purified by silica gel column chromatography (chloroform:methanol = 20:1) to give (84α) [9.26 g (yield 59.4%)] as white powder, yellow powder (3.99 g) and the starting material (6) recovered [1.72 g (24.6% recovery)]. Recrystallization of 84α from ethyl acetate gave 84α as white crystals (5.89 g). Purification of yellow powder (3.9 g) by HPLC (silica gel cartridge column, eluent chloroform: methanol = 100:1 → 50:1) gave 84β as white powder [1.80 g (yield 11.6%)].

Compound 84α (crystals)

[0130]

$C_{42}H_{56}FNO_{17}$
MW = 865.90
MP = 156°C
FAB(+)MS 866 $(M+H)^+$

IRv^{KBr} cm^{-1} : 3520 (OH,NH)
1749, 1666 (C=O)
1624 (C=C)
1540 (NH)
1039 (C-O)

^{1}H-NMR [500MHz, $CDCl_3$, Ref=0.000 ppm (TMS)]

δ : 0.926 (3H, d, J-7.3Hz, 16-CH_3)
1.015 (3H, s, CH_3)
1.537 (3H, s, CH_3)
1.877, 2.029, 2.044, 2.148, 2.159 (each 3H, 5s, 5Ac)
2.794 (1H, dd, J=4.8, 12.8Hz, H-$3_{eq\ NeuNAc}$)
3.748 (1H, dd, J=2.2, 10.6Hz, H-6_{NeuNAc})
3.788 (1H, s, $COOCH_3$)
4.022 (1H, dd, J = 5.9, 12.5 Hz, H-9_{NeuNAc})
4.029 (1H, t, J = 10.6Hz, H-5_{NeuNAc})
4.261 (1H, dd, J = 2.6, 12.5 Hz, H'-9_{NeuNAc})
4.278 (1H, d, J = 18.7Hz, H-21)
4.920 (1H, ddd, J = 4.8, 10.6, 12.1Hz, H-4_{NeuNAc})
5.105 (1H, d, J = 18.7Hz, H'-21)
5.121 (1H, d, J = 9.9Hz, NH)
5.285 (1H, dd, J = 2.2, 9.5Hz, H-7_{NeuNAc})
5.474 (1H, ddd, J = 2.6, 5.9, 9.5Hz, H-8_{NeuNAc})
6.106 (1H, s, H-4)
6.324 (1H, dd, J = 1.8, 10.3 Hz, H-1)
7.212 (1H, d, J = 10.3Hz, H-2)

81+6 →84α+84β

Compound 84β (crystals)

[0131]

$C_{42}H_{56}FNO_{17}$
MW = 865.90
MP = 194 - 197°C
FAB (+) MS 866 $(M+H)^+$, 888 $(M+Na)^+$
^{1}H-NMR [500 MHz, $CDCl_3$, Ref = 0.000ppm(TMS)]

δ ; 0.857 (3H, d, J = 7.3 Hz, 16-CH_3)
1.031 (3H, s, CH_3)
1.547 (3H, s, CH_3)
1.896, 1.995, 2.027, 2.044, 2.153 (each 3H, 5s, 5Ac)
2.553 (1H, dd, J = 5.1, 12.8 Hz, H-$3_{eq\ NeuNAc}$)
3.885 (1H, dd, J = 10.3, 12.8Hz, H-9_{NeuNAc})
4.093 (1H, q, J = 10.3Hz, H-5_{NeuNAc})
4.378 (1H, dd, J = 2.2, 10.3 Hz, H-5_{NeuNAc})
4.498 (1H, d, J = 17.6Hz, H-21)
4.796 (1H, d, J = 17.6Hz, H'-21)
5.114 - 5.156 (2H, m, H-8_{NeuNAc} + H'-9_{NeuNAc})
5.379 (1H, t, J = 2.2Hz, H-7_{NeuNAc})
5.399 (1H, dt, J = 5.1, 10.3Hz, H-4_{NeuNAc})
5.520 (1H, d, J = 10.3Hz, NH)
6.113 (1H, s, H-4)
6.331 (1H, dd, J = 1.8, 10.3 Hz, H-1)
7.211 (1H, d, J = 10.3Hz, H-2)
IR ν^{KBr} cm^{-1} : 3572, 3494 (OH,NH)
1767, 1755, 1735, 1663(C=O)
1625, 1605 (C=C)

2) Synthesis of a deprotected derivative of sialyldexamethasone (α)

[0132] 84α [2.98 g (3.45 mmol)] was dissolved in methanol (20 ml), and to this solution was added 1 M sodium methoxide (0.7 ml) at 0°C. The mixture was stirred at room temperature for 2 h. The solvent was distilled off from the reaction mixture *in vacuo*, and to the residual material were added water (10 ml) and 1 M sodium methoxide (3.4 ml).

The mixture was stirred at room temperature for 30 min. Then the reaction solution was applied to a gel filtration column of LH-20, and eluted with methanol. The solvent was distilled off from fractions containing product *in vacuo* to give 85α as white powder [2.30 g (94.7%)]. 85α was further recrystallized from methanol to give colorless crystals (1.20 g).

Compound 85α (crystals)

[0133]

$C_{33}H_{45}FNO_{13}Na$
MW = 705.71
MP = 214°C (decomp.)
FAB (+)MS 706 $(M+H)^+$, 728 $(M+Na)^+$

IR ν^{KBr} cm^{-1} : 3374 (OH,NH)
1727, 1664 (C=O)
1615 (COONa)
1559 (NH)
1069, 1041 (C-O)

^{1}H-NMR [500 MHz, CD_3OD, Ref = 0.000ppm(TMS)]

δ ; 0.839 (3H, d, J = 7.3 Hz, 16-CH_3)
1.008 (3H, s, CH_3)
1.583 (3H, s, CH_3)
1.705 (1H, t, J = 12.1Hz, H-$3_{ax\ NeuNAc}$)
2.010 (3H, s, Ac)
2.880 (1H, dd, J = 4.4, 12.1 Hz, H-$3_{eq\ NeuNAc}$)
3.442 (1H, dd, J = 2.2, 9.2Hz, H-7_{NeuNAc})
3.597 (1H, dd, J = 6.6, 11.4 Hz, H-9_{NeuNAc})
3.836 (1H, dd, J = 2.2, 11.4 Hz, H'-9_{NeuNAc})
3.905 (1H, ddd, J = 2.2, 6.6, 9.2Hz, H-8_{NeuNAc})
4.595 (1H, d, J = 18.7Hz, H-21)
4.683 (1H, d, J = 18.7Hz, H'-21)
6.068 (1H, s, H-4_{NeuNAc})
6.281 (1H, dd, J = 1.8, 10.3 Hz, H-1)
7.408 (1H, d, J = 10.3Hz, H-2)

84α→85α

3) Synthesis of a deprotected derivative of sialyldexamethasone (β)

[0134] 84β [506.1 mg (0.584 mmol)] was dissolved in methanol (50 ml), and to this solution was added 1 M sodium methoxide (0.7 ml). The mixture was stirred at room temperature for 2 h. The solvent was distilled off from the reaction solution *in vacuo*, and to the residue were added water (3 ml), 1 M sodium methoxide (0.58 ml) and methanol (1 ml). The resulting mixture was stirred at room temperature for 1 h. Then the reaction solution was applied to a gel filtration column of LH-20, and eluted with methanol. The solvent was distilled off from fractions containing product *in vacuo* to give 85β as white powder [389.3 mg (yield 94.5%)].

Compound 85β

[0135]

$C_{33}H_{45}FNO_{13}Na$
MW = 705.71
MP = 228 - 229 °C (decomp.)
FAB (+) MS 706 $(M+H)^+$, 728 $(M+Na)^+$
^{1}H-NMR [500 MHz, CD_3OD, Ref = 0.000ppm(TMS)]

δ ;	0.826 (3H, d, J = 7.3 Hz, 16-CH_3)
	1.001 (3H, s, CH_3)
	1.587 (3H, s, CH_3)
	1.979 (3H, s, Ac)
	2.448 (1H, dd, J = 5.1, 12.8 Hz, H-$3_{eq\ NeuNAc}$)
	3.408 (1H, d, J = 10.3Hz, H-6_{NeuNAc})
	3.643 (1H, dd, J = 5.1, 11.4 Hz, H-9_{NeuNAc})
	3.714 (1H, d, J = 10.3Hz H-7_{NeuNAc})
	3.787 (1H, dd, J = 2.9, 11.4Hz, H'-9_{NeuNAc})
	3.950 (1H, t, J = 10.3Hz, H-5_{NeuNAc})
	4.109 (1H, dt, J = 5.1, 10.3Hz, H-4_{NeuNAc})
	4.300 (1H, d, J = 18.3Hz, H-21)
	4.611 (1H, d, J = 18.3Hz, H'-21)
	6.068 (1H, s, H-4)
	6.289 (1H, dd, J = 1.8, 9.9Hz, H-1)
	7.419 (1H, d, J = 9.9Hz, H-2)
IR ν^{KBr} cm^{-1} :	3400 (OH, NH)
	1721, 1663(C = O)
	1623(COONa)
	1560(NH)
	1067, 1023(C- O)

84β→85β

Example 11

Synthesis of sialylbetamethasone (Fig. 11)

1) Sialylbetamethasone (glycosylation)

[0136] Betamethasone (86) (1.0 g) was dissolved in tetrahydrofuran (20 ml), and to this solution were added silver triflate (1.31 g) and molecular sieve 5A (1.0 g). To this mixture was added, under an argon atmosphere and at - 40°C, a solution of methyl 2-chloro-4,7,8,9-tetra-O-acetyl-N-acetylneuraminate (81) (2.08 g) in terahydrofuran. While the reaction temperature was slowly raised to room temperature, the mixture was stirred for 5 h. The reaction solution was filtered, and the solvent was distilled off from the filtrate *in vacuo*. The residue was dissolved in chloroform, and the solution was washed with saturated sodium chloride solution. After the chloroform solution was dried over anhydrous magnesium sulfate, the solvent was distilled off *in vacuo*. The residue thus obtained was purified by silica gel column chromatography (chloroform:methanol = 15:1), and further purified by Lobar column using silica gel column (diisopropyl ether:methanol = 5:1) to give 87 as white powder [953.9 mg (yield 43.4%)].

81 + 86 → 87

Compound 87

[0137]

$C_{42}H_{56}FNO_{17}$ MW = 865.90

^{1}H-NMR [500 MHz, $CDCl_3$, Ref 0.00ppm (TMS)]

• NeuAc

3 eq	2.813 (1H, dd, $J_{3ax\ \cdot\ 3eq}$ = 4.76, $J_{3eq\ \cdot\ 4}$ = 12.46)
4	4.896 (1H, ddd, $J_{4,5}$ = 10.26)
5	4.058 (1H, t, $J_{5,6}$ = 10.63)
6	3.727 (1H, dd, $J_{6,7}$ = 2.19)
7	5.302 (1H, dd, $J_{7,8}$ = 9.90)
8	5.483 (1H, ddd, $J_{8,9}$ = 2.93)
9	4.251 (1H, dd, $J_{9,9'}$= 12.45)
9'	4.014 (1H, dd, $J_{8,9'}$= 6.22)

OAc x 5 2.151, 2.044, 2.025, 1.868 (15H, s)
$COOCH_3$ 3.822 (3H, s)

IR ν^{KBr} cm^{-1} 3500(O-H), 1748(C = O position-20), 1663(C=O position-3)
FAB (+) MS 866$(M+H)^+$, 806$(M-COOCH_3)^+$
MP : 145 - 148°C

2) Deprotection of a protected derivative of sialylbetamethasone

[0138] 87 (402 mg) was dissolved in methanol (4 ml), and to this solution was added 1 M sodium methoxide (0.45 ml) at 0 - 5°C. The mixture was stirred at room temperature for 3 h. After the solvent of the reaction solution was evaporated *in vacuo*, water (2 ml) and 1 M sodium methoxide (0.46 ml) were added to the residue, and the resulting mixture was stirred at room temperature for 30 min. The reaction solution was applied to to a gel filtration column of LH-20, and eluted with methanol. The solvent was distilled off from fractions containing product *in vacuo* to give pale yellow powder (329.4 mg). A portion of the yellow powder (269 mg) was purified by HPLC using a reversed phase partition column (acetonitrile-water) to give 89β [32.4 mg (yield 12.5%)] and 89α [134 mg (yield 51.7%)], respectively, both as white powder.

[0139] Furthermore, a remaining portion of the product (60 mg) was treated with activated carbon to give 90 [38.0 mg (yield 63.7%)] as yellowish white powder.

Compounds 89β , 89α and 90

[0140]

Compounds 89β and 89α $C_{33}H_{46}FNO_{13}$ MW = 683.723
Compound 90 $C_{33}H_{46}FNO_{13}Na$ MW = 705.704

Compound 89β

[0141]

^{1}H-NMR [500 MHz, CD_3OD, Ref = 3.30ppm (CH_3OD)]

3_{ax}	1.689 (1H, dd, $J_{3ax \cdot 4}$ = 11.36, $J_{3ax \cdot 3eq}$ = 12.82)
3_{eq}	2.432 (1H, dd, $J_{3eq \cdot 4}$ = 5.12)
4	4.164 (1H, ddd, $J_{4,5}$ = 10.99)
5	3.832 (1H, t, $J_{5,6}$ = 10.25)
6	3.602 (1H, dd, $J_{6,7}$ = 11.36)
9	3.745 (1H, dd, $J_{9,8}$ = 5.50, $J_{9,9'}$ = 9.53)
9'	3.462 (1H, dd, $J_{9,9'}$ = 9.53)
Ac	2.004 (3H, s)

FAB(-)MS 682$(M-H)^+$

Compound 89α

[0142]

^{1}H-NMR [500 MHz, DMSO, Ref = 2.50ppm(DMSO)]

3_{ax}	1.530 (1H, d, $J_{3ax \cdot 3eq}$ = 12.46)
3_{eq}	2.561 (1H, dd, $J_{3eq \cdot 4}$ = 4.40)

FAB(-)MS 682 $(M-H)^+$
MP : 156 - 159°C

Compound 90

[0143]

FAB(-)MS 704 $(M-H)^+$
^{1}H-NMR [500 MHz, CD_3OD, Ref = 3.30ppm (CH_3OD)]

1 :	6.066 (1H, s)
3ax :	1.711 (1H, t, J = 12.09)
3eq :	2.378 (1H, t, J = 4.03)

Example 12

Synthesis of glucosylbetamethasone (protected derivative: per-Tol) (Fig. 12)

3 + 86 → 91 (glucosylation)

[0144] Betamethasone (86) (3.69 g) was dissolved in tetrahydrofuran (200 ml), and to this solution were added molecular sieve 5A (4.90 g) and silver triflate (4.83 g). To this mixture was added, under an argon atmosphere and at 0 - 5°C, a solution of a glucose bromide (protected derivative: per-Tol) (3) (13.45g) dissolved in tetrahydrofuran (70 ml). While the reaction temperature was raised slowly to room temperature, the mixture was stirred for 6 h. To this mixture was further added silver triflate (4.83 g), and the resulting mixture was stirred overnight. The reaction solution was filtered, and the solvent was distilled off from the filtrate *in vacuo*. The residue was dissolved in chloroform, and the chloroform solution was washed saturated sodium chloride solution. After the chloroform solution was dried over anhydrous magnesium sulfate, the solvent was distilled off *in vacuo*. The residue thus obtained was purified by silica gel chromatography (toluene:ethyl acetate = 3:1) to give white powder [2.87 g(yield 29.7%)]. This product was further purified by HPLC using a reversed phase partition column to give 91β [1.46 g (yield 15.1%)] and 91α [0.17 g (yield 1.8%)], respectively, both as white powder.

Compound 91 [glucosylbetamethasone (protected derivative: per Tol)]

[0145]

Molecular formula $C_{60}H_{63}FO_{14}$
MW 1027.148

Glucosylbetamethasone (per Tol) β-anomer (91β)

[0146]

^{1}H-NMR [500 MHz, $CDCl_3$, Ref = 0.000ppm(TMS)]

1:	5.012 (1H, d, $J_{1,2}$ = 8.06)
2:	5.516 (1H, t, $J_{2,3}$ = 9.89)
3:	5.872 (1H, t)
4:	5.642 (1H, t)
5:	4.097 (1H, t)
($CH_3C_6H_4CO$-) x 4 :	7.865, 7.830, 7.782, 7.716 (each 2H, d)
($CH_3C_6H_4CO$-) x 4 :	2.380, 2.347, 2.286 (12H, s)

IR ν^{KBr} cm^{-1} 3472(O-H), 1732(C = O position-20), 1665(C=O position-3)
FAB(+)MS 1027$(M+H)^+$, 1009$(M-OH)^+$
MP : 154 - 157°C

Glucosylbetamethasone (per Tol) α-anomer (91α)

[0147]

^{1}H-NMR [500 MHz, $CDCl_3$, Ref = 0.000ppm(TMS)]

1:	5.254 (1H, d, $J_{1,2}$ = 4.03)
2:	5.205 (1H, dd, $J_{2,3}$ = 10.25)
3:	6.120 (1H, t)
4:	5.741 (1H, t)
6:	4.926 (1H, dd, $J_{6,6'}$ = 12.46)
6':	4.223 (1H, dd, $J_{5,6'}$ = 2.56)
($CH_3C_6\underline{H}_4CO$-) x 4 :	7.946, 7.872, 7.835, 7.764 (each 2H, d)
($C\underline{H}_3C_6H_4CO$-) x 4 :	2.419, 2.366, 2.334, 2.294 (each 3H, s)

IR ν^{KBr} cm^{-1} 3478(O-H), 1731(C = O position-20), 1666(C=O position-3)
FAB(+)MS 1027$(M+H)^+$, 1009$(M-OH)^+$
MP : 159 - 162°C

(II) Evaluation of pharmacological activity

[0148] Ointment to be tested was prepared using white soft paraffin as the base and containing dexamethasone at 0.1% concentration.

1. Inhibitory effects on Granuloma growth (paper disk method)

1) Experimental method

[0149] Groups of 5 male Sprague-Dawley rats each weighing 150 - 170 g were used. Under ether anesthesia, the dorsum of animals was closely clipped, and medianly incised. After each one pre-weighed paper disk (8-mm diameter, 1-mm thick, weighing about 30 mg; Toyo-Roshi filter paper) was inserted subcutaneously into both sides of the dorsal incision, the incision was sutured. In order to prevent bacterial infection, penicillin G potassium salt (2,000 units) per rat was intramascularly injected after the surgery. Base or ointment to be tested (50 mg each) was rubbed carefully into the skin over the paper disk inserted site, for 30 seconds once a day for the duration of 7 days. Rats were slipped plastic cangs on to prevent them from licking the drug applied sites. On the 8th day of the test, rats were sacrificed under ether anesthesia, and granulomas were carefully excised. Granulomas were dried at 40°C for 24 h, and their dry weights were recorded.

2) Results

[0150] Inhibitory effects of dexamethasone derivatives on the weight increase of granuloma of experimental animals as compared with those of control animals are shown as per cent of inhibition over the control in Table 1. Figures with asterisks in the table indicate significant difference. The same will be applied to the following other tables.

Table 1

Effects of dexamethasone derivatives on growth of granuloma

Test compound	Weight of granuloma
Control	0.0±5.8
White soft paraffin (base)	-0.6±6.1
Betamethasone valerate	-22.5±5.7*
Dexamethasone	-42.2±2.6**
4α	-0.6±5.1
4β	-7.9±5.0
5β	-47.4±2.9**
10	-38.3±5.3**
14α	5.7±1.9
14β	-8.7±7.2
15α	-39.5±1.8**
15β	-41.0±2.6**
24α	-3.7±4.5
25α	-18.0±4.8*
29	-35.7±5.6**
34β	-21.3±3.9*
35β	-21.9±4.2*
44β	-16.5±3.0*
44'	3.3±4.7
45β	-28.1±3.5**

Test compound	Weight of granuloma
45'	-11.8±10.1
54β	-35.1± 2.8**
54'	-44.8± 2.4**
55β	-37.4±7.1**
59β	-7.7± 6.8
64β	-32.5± 0.5**
64'	-41.3± 2.3**
65β	-33.0± 3.3**
66	-29.3± 6.3**
69β	0.7± 2.4
74β	1.6±16.2
75β	-10.0± 8.8
84α	-16.0± 2.9
84β	-7.3± 3.8
85α	-31.1± 2.2**
85β	-7.8± 5.2
87	1.2± 6.1
89α	-22.1± 6.0*
89β	-26.4± 2.2**
90	-13.1± 4.7

Test compound	Weight of granuloma
Control	0.0±5.1
White soft paraffin (base)	-0.7±7.1
Betamethasone valerate	-19.4±4.8
Dexamethasone	-55.4±5.7
105β	-1.2±5.7
107β	-6.3±5.5
109β	-0.2±3.7

Figures indicate the per cent of inihibition over granuloma weights of the controls.

2. Croton oil-induced granuloma

1) Experimental method

[0151] Groups of 5 male Sprague-Dawley rats each weighing 160 - 180 g were used. Under ether anesthesia, the dorsum of animals was closely clipped, and air sac was formed by injecting air (20 ml) subcutaneously. Next day cotton seed oil containing 1% croton oil was injected into the air sac. Drugs to be tested were suspended in the cotton seed oil containing 1% croton oil, and administered. After 7 days, the blood was taken from the animal under ether anesthesia. Then, the granuloma pouch fluid (exudate) was collected, and the fluid volume was measured. The pouch wall formed around granuloma and thymus were also excised and weighed.

2) Results

[0152] Per cent of inhibition over the volume of pouch fluid, and wet weight of granuloma pouch as well as thymus of the control are shown in Tables 2 - 4.

Table 2

Effects of dexamethasone derivatives on croton oil-induced granuloma Effects on pouch fluid (exudate) volume			
Test compound	0.01mg/rat	0.1mg/rat	1.0mg/rat
Betamethasone valerate	21.3±10.8	1.3±6.3	23.9±12.1
91β	25.3± 5.3	18.4±6.1	18.9± 8.8
100β	20.8±11.7	17.5±5.9	69.4± 6.7
103β	32.8± 9.6	24.8±4.8	43.2± 6.9
Test compound	0.01mg/rat	0.1mg/rat	1.0mg/rat
Betamethasone valerate	-6.4±16.1	14.0± 6.5	41.0± 9.9
Diflupredonate	17.4±13.5	65.3±12.1	96.2± 1.2
Diflurasone acetate	-20.9±13.8	-14.5±11.6	14.3±15.1
Diflucortolone valerate	27.3± 6.7	48.9± 2.9	90.8± 3.3
105β	-8.1± 9.4	24.8± 8.8	76.4± 4.3
107β	-28.5±18.8	-30.9±20.9	28.8±15.2
109β	-13.1±16.7	14.6± 9.4	37.5±11.9
Test compound	0.1mg/rat	1.0mg/rat	10.0mg/rat
Betamethasone valerate	14.3±7.6	46.2±5.8	----
Betamethasone acetate propionate	27.6±8.1	43.6±4.7	----
Diflucortolone valerate	48.3±6.1	92.4±2.1	----
109β	26.6±4.2	61.3±2.9	90.8±1.6
110β	34.4±8.0	73.6±2.1	97.2±0.5
112β	36.1±9.2	43.7±2.5	93.1±1.6
113β	90.5±6.6	97.1±0.5	97.5±0.7
Figures indicate the per cent of inhibition over the pouch fluid volume of the control.			

Table 3

Effects of dexamethasone derivatives on croton oil-induced granuloma Effects on granuloma weight			
Test compound	0.01mg/rat	0.1mg/rat	1.0mg/rat
Betamethasone valerate	25.0±5.1	10.2± 5.2	18.7±11.7
91β	17.1±6.7	6.9± 5.1	4.3± 8.2
100β	11.0±6.5	4.1±11.3	60.5± 5.8
103β	25.9±8.6	15.0± 7.0	34.5± 6.4
Test compound	0.01mg/rat	0.1mg/rat	1.0mg/rat
Betamethasone valerate	-7.0±14.3	0.4± 9.4	23.6±10.1
Diflupredonate	-11.0±23.1	35.0±10.3	78.8± 5.0
Diflurasone acetate	-13.1±13.3	4.0±10.5	11.7±12.4
Diflucortolone valerate	12.8± 5.1	22.1± 3.6	66.0± 7.1
105β	-5.9±10.9	22.1± 3.7	53.0± 6.2
107β	-21.2±19.2	-23.3±21.4	28.1±12.5
109β	-21.3±13.5	6.0± 9.3	36.5±10.2
Test compound	0.1mg/rat	1.0mg/rat	10.0mg/rat
Betamethasone valerate	8.1± 7.0	36.4±4.4	----
Betamethasone acetate propionate	21.2± 6.4	26.0±6.9	----
Diflucortolone valerate	25.1± 5.0	66.4±3.3	----
109β	13.5± 4.4	44.7±3.6	58.0±1.9
110β	16.8± 7.1	58.7±1.4	70.3±1.9
112β	15.9± 6.9	27.1±2.4	61.3±2.2
113β	47.4±11.0	60.8±9.3	90.5±0.6
Figures indicate the per cent of inhibition over the granuloma weight of the control.			

Table 4

Effects of dexamethasone derivatives on croton oil-induced granuloma Effects on thymus weight			
Test compound	0.01mg/rat	0.1mg/rat	1.0mg/rat
Betamethasone valerate	-0.5±5.8	7.3±4.1	37.0±3.0
91β	2.1±3.7	7.4±2.8	4.7±9.7
100β	6.3±4.8	0.1±4.5	1.8±6.2
103β	21.5±5.7	11.2±3.1	4.3±3.9
Test compound	0.01mg/rat	0.1mg/rat	1.0mg/rat
Betamethasone valerate	1.7± 6.3	13.5±5.8	58.9±3.3
Diflupredonate	14.7±10.4	71.2±2.9	71.8±3.2
Diflurasone acetate	3.9± 9.0	32.4±4.5	55.5±7.7
Diflucortolone valerate	31.6± 6.4	70.6±3.4	77.3±3.8
105β	-1.9± 7.8	-2.0±8.6	-5.0±5.2
107β	-4.2± 5.5	3.9±5.9	-4.9±7.2
109β	-2.7± 7.5	-6.0±9.6	3.4±8.6
Test compound	0.1mg/rat	1.0mg/rat	10.0mg/rat
Betamethasone valerate	22.3± 1.6	50.1±6.0	----
Betamethasone acetate propionate	16.7±14.1	56.3±3.6	----
Diflucortolone valerate	80.1± 2.5	81.4±2.4	----
109β	10.9± 8.6	17.7±4.6	15.9±3.3
110β	20.9± 6.3	22.9±8.4	19.5±8.3
112β	13.7± 7.3	20.5±5.7	15.7±9.2
113β	78.9± 3.2	95.8±0.8	94.8±0.6
Figures indicate the per cent of inhibition over the control thymus weight.			

[0153] Results shown in Tables 2 - 4 confirmed that the compounds of the present invention have inhibitory effects on the growth of granuloma in rats.

[0154] That is, results in Tables 2 - 4 indicate that the compounds of the present invention have the following pharmacological properties.

1) Effects on thymus weight are significantly reduced with the glucosyl derivatives as compared with the non-glucosylated original compounds or the conventional anti-inflammatory drugs.
2) Reducing effects on the thymus atrophy were clearly observed with the glucosylated derivatives protected with toluoyl, benzoyl and chlorobenzoyl groups, but not with those protected with acetyl group.
3) Suppression effects of glucosyl derivatives on granuloma weights and pouch exudate volumes were lower than those of the non-glycosylated compounds, but more highly effective than those of the conventional drugs.

3. Inhibitory effects on croton oil-induced ear lobe edema

1) Experimental method

[0155] Groups of 10 male ddY mice each weighing about 25 g were used. Ointment to be tested (20 mg) was

rubbed in the right-side ear lobe, and, 30 min later, a drop of 4% croton oil dissolved in ether was applied to it. Thirty minute after that treatment, mice were sacrificed. Ear lobes on both sides were punched out in the size of 5-mm diameter, and weighed. Results were expressed by calculating the per cent of weight change of the right edema ear as compared with that of the untreated left ear, and compared with that of the control.

2) Results

[0156] Per cent of inhibition of edema formation in experimental mice as compared with those of controls are shown in Tables 5 and 6.

Table 5

Effects of dexamethasone derivatives on croton oil-induced ear edema

Test compound	Per cent of inhibition of ear edema (%)
Control	0.0±5.3
White soft paraffin (base)	1.6±4.9
Betamethasone valerate	29.1±5.9**
Dexamethasone	32.9±3.5**
4α	24.1±4.9**
4β	23.5±4.1**
5β	19.6±3.3**
10	27.5±5.9**
14α	9.0±4.9
14β	11.9±3.5
15α	27.5±3.6**
15β	34.0±4.1**
24α	6.8±2.9
25α	24.9±5.5**
29	22.1±4.7**
34β	9.1±5.0
35β	29.0±3.0**
44'	7.9±7.2
44β	9.2±4.5
45'	21.0±6.4*
45β	24.6±6.3**
54'	25.7±4.1**
54β	13.2±5.1
55β	21.6±5.9*
59β	13.6±4.0
64'	18.4±4.5*
64β	17.7±2.8**
65β	26.5±3.2**
66	18.3±3.6*
69β	17.8±3.8*
75β	22.0±4.7**
74β	14.1±4.5
84α	13.6±3.6*
84β	11.0±4.8
85α	26.5±4.4**
85β	19.2±3.7**
87	8.8±5.0
89α	22.5±5.2**
89β	22.2±5.3**
90	15.6±6.6

Figures indicate the per cent of inhibition over the edema formation in the control.

Table 6

Effects of dexamethasone derivatives on croton oil-induced ear edema	
Test compound	Per cent of inhibition of ear edema (%)
Control	0.0±7.3
White soft paraffin (base)	7.4±6.3
Betamethasone valerate	24.9±3.5
Dexamethasone	32.9±3.5
91β	32.9±7.8
94β	35.1±4.1
97β	36.6±5.1
100β	40.5±4.7
105β	42.0±2.9
107β	41.4±6.1
109β	38.6±9.2
114β	49.8±9.7
115β	23.3±2.1
117β	24.2±6.3
Figures indicate the per cent inhibition to the edema formation in controls.	

[0157] Results in Tables 5 and 6 confirmed that the compounds of the present invention have inhbitory effects on the croton oil-induced ear edema in mice.

4. Effects of 7-day ointment rubbing on organ weights

1)Experimental method

[0158] Groups of 5 male Sprague-Dawley rats each weighing 150 - 170 g were used. Under ether anesthesia, the dorsum of animals were closely clipped, and test drug (100 mg) was carefully rubbed in the clipped dorsal area for 30 seconds. Rats were slipped on plastic cang to prevent them from licking the drug-applied area. After the drug rubbing once daily for 7 days, on the 8th day rats were anesthetized with ether. Blood samples were collected, and thymus, spleen, and adrenal were excised and measured their wet weights. Furthermore, leukocyte number was counted with the blood samples collected. Results were expressed as the per cent of change of body weight on the 8th day as compared with that on the 1st day of rubbing. Similarly, the per cent of change in weights of thymus, spleen and adrenal on the 8th day as compared with that of the control animals were shown.

2. Results

[0159] Effects of 7-day ointment rubbing on weights of body, thymus, spleen and adrenal, and leukocyte counts are shown in Tables 7 and 8.

Table 7

Effects of 7-day rubbing of dexamethasone derivatives on body weight, organ weight and leukocyte count

Test compound	Body weight	Adrenal weight	Thymus weight	Spleen weight	Leukocyte count
Normal animal	23.2± 1.7	0.0± 5.6	0.0± 2.2	0.0± 3.4	0.0± 6.3
White soft paraffin (base)	22.2± 0.6	-1.8± 4.5	-6.0± 7.5	13.1± 5.5	-20.3±11.9
Betamethasone valerate	23.8± 2.7	-12.8± 2.2**	-23.3± 3.4**	-10.9± 5.8	1.5± 3.0
Dexamethasone	-8.7± 1.4**	-48.5± 1.4**	-91.5± 0.6**	-70.0± 3.5**	-46.5±12.1**
4α	27.2± 0.9*	-13.8± 2.3*	3.1± 8.9	9.9± 6.0	3.2± 4.5
4β	21.4± 1.8**	-15.3± 3.0*	0.6± 5.9	1.9± 4.3	19.0± 4.7
5β	0.7± 1.4**	-49.6± 3.2**	-85.7± 2.6**	-56.0± 1.6**	-46.6± 3.2**
10	-2.7± 2.6**	-53.8± 3.5**	-85.5± 3.8**	-68.5± 2.8**	-54.9± 4.3**
14α	25.2± 0.8**	-11.0± 5.7	-10.7± 8.5	-5.5± 7.1	-21.8±10.5
14β	25.3± 1.6*	-9.5± 4.8	-12.0± 2.2	0.5± 5.1	-0.6± 6.1
15α	8.3± 1.0**	-48.3± 2.9**	-82.2± 3.3**	-35.7± 2.3**	-22.6± 7.4*
15β	4.6± 0.9**	-47.1± 1.9**	-86.0± 1.4**	-43.2± 2.1**	-37.0± 6.9**
24α	22.7± 1.9**	-7.8± 8.3	-15.1±11.4	-2.0± 7.3	-4.3± 9.4
25α	16.1± 1.7*	-24.4± 3.4**	-32.6± 7.4**	-18.2± 2.2**	-0.7± 9.0
29	-1.1± 2.0**	-46.0± 2.4**	-88.8± 2.2**	-59.5± 1.6**	-55.5± 4.9**
34β	11.9± 1.0**	-37.4± 3.9**	-66.4± 1.1**	-37.2± 1.8**	-43.7± 6.7**
35β	10.5± 2.8**	-29.9± 5.0**	-61.9± 3.1**	-28.7± 5.5**	-36.4± 4.7**
44*	22.7± 1.1**	-19.6± 5.5*	-17.9± 3.3*	-11.5± 4.8	-23.0± 5.1
44β	12.4± 2.7**	-33.0± 4.6**	-57.2± 9.5**	-35.4± 4.9**	-20.7± 7.0
45*	22.9± 1.7	-15.4± 3.2*	-6.8± 4.0	-0.1± 5.1	6.6±15.1
45β	13.3± 3.1*	-37.6± 2.8**	-55.1± 7.9**	-24.2± 5.3**	-22.3± 4.5*
54*	-0.8± 1.6**	-50.1± 3.0**	-87.6± 3.0**	-63.2± 3.1**	-57.2± 6.0**
54β	13.6± 1.6**	-41.7± 5.1**	-64.6± 6.3**	-41.3± 1.7**	-35.1± 4.8*
55β	12.4± 2.7*	-42.5± 3.7**	-69.9± 5.5**	-26.8±11.0*	-43.3± 4.4**
59β	24.4± 1.2**	-17.4± 3.9*	-17.5±10.3	0.0± 6.6	11.8± 5.7
64*	-0.9± 2.0**	-50.1± 2.3**	-89.6± 2.0**	-61.9± 2.6**	-57.2± 2.9**
64β	7.8± 1.5**	-46.0± 4.1**	-86.5± 1.4**	-47.6± 2.0**	-48.3± 4.8**
65β	13.9± 2.1**	-32.0± 2.9**	-47.1± 9.9**	-21.3± 4.0**	-20.3±19.7
66	14.3± 1.6**	-28.8± 3.0**	-39.0± 5.2**	-19.4± 2.2**	-25.9±13.8
69β	26.3± 2.0	-3.9± 3.9	-16.5± 8.6	-4.4± 4.7	6.9± 9.3
74β	19.4± 2.1**	-24.6± 3.7**	-26.3± 5.6*	-9.1± 4.6	6.6± 8.4
75β	22.5± 2.5	-48.9±10.6**	-21.3± 8.9**	3.5± 4.2	19.3± 9.5
84α	24.8± 1.7*	-19.7± 3.5**	-16.4± 6.2	-15.2± 3.6*	-5.5±13.5
84β	26.6± 3.1	-17.6± 2.1**	-13.5± 4.9	-5.0±11.1	2.3±13.3
85α	12.9± 2.7*	-40.9± 2.0**	-58.3± 6.7**	-27.8± 3.5**	-25.2± 3.3**
85β	14.1± 2.3*	-33.4± 5.2**	-53.1± 7.5**	-16.1± 8.9	-32.5± 9.4*
87	23.5± 1.5**	-12.1± 3.5*	-10.8± 5.8	-1.3± 4.6	-10.3±12.5
89α	19.6± 1.5	-22.7± 1.8**	-18.5± 6.8*	-7.2± 2.9	18.7± 8.7
89β	16.7± 1.8*	-21.7± 3.1**	-33.1± 8.8**	-13.6± 2.7*	-6.6± 6.8
90	21.7± 1.6	-22.9± 3.7**	-9.2± 6.3	0.1± 4.4	12.8± 8.8

Table 8

Effects of 7-day rubbing of dexamethasone derivatives on body weight, organ weight and leukocyte count					
Test Compound	Body Weight	Adrenal weight	Thymus weight	Spleen weight	Leukocyte count
Normal animal	30.5±1.3	0.0±2.4	0.0±4.1	0.0±5.4	0.0± 8.6
White soft paraffin (base)	28.2±0.6	-1.8±4.5	-6.0±7.5	13.1±5.5	-20.3±11.9
Betamethasone valerate	18.1±1.6	-26.9±5.5	-57.2±5.1	-28.8±3.7	-44.7± 3.8
Dexamethasone	-8.8±3.4	-49.2±3.7	-91.9±0.9	-71.6±2.1	-61.1± 3.3
105β	22.4±1.0	0.7±4.5	0.6±4.4	6.7±2.6	-10.6± 6.2
107β	27.6±2.2	-5.7±2.6	2.8±6.7	8.8±3.6	-20.3±14.4
109β	27.6±3.2	-0.8±1.8	14.1±5.9	-0.9±5.7	-29.2± 9.9

[0160] Results shown in Tables 7 and 8 confirmed that the compounds of the present invention are less toxic and pharmacologically more safe than dexamethasone.

[0161] As aforementioned, a series of steroid compounds of the present invention have the pharmacological effects shown in Tables 2 - 8, respectively. Among them, particularly, glycosyl steroid derivatives with Tol-protecting group including gulcosyl dexamethasone protected with Tol group and β-galacturonyldexamethasone protected with Tol group not only have suppressing effects on granuloma growth and croton oil-induced ear edema, but also they are less toxic and highly more safe.

Example 13

Synthesis of glucosylbetamethasone (*p*-toluoyl derivative) (modified method) (Fig. 13)

1) Synthesis of glucosylbetamethasone (*p*-toluoyl derivative) (91) 3 + 86 → 91

[0162] Betamethasone (86) (1.28 g) was dissolved in acetonitrile (85 ml), and to this solution were added molecular sieve 3A (1.80 g) and silver triflate (1.62 g). To this mixture was added, under an argon atmosphere and at 0 - 5°C, a solution of a glucose bromide (3) (4.65 g) dissolved in acetonitrile (45 ml). While the reaction temperature was slowly raised to room temperature, the resulting mixture wash stirred for 6 h. To this mixture was further added silver triflate (1.62 g), and the resulting mixture was stirred at room temperature for 19 h. The reaction solution was filtered, and the solvent was distilled off from the filtrate *in vacuo*. The residue was dissolved in chloroform, and the solution was washed with saturated sodium chloride solution. After the chloroform solution was dried over anhydrous magnesium sulfate, the solvent was evaporated *in vacuo*. The residue thus obtained was purified by silica gel column chromatography (hexane:ethyl acetate = 5:4) to give white powder (2.62 g). This powder was further purified by HPLC using a reversed phase partition column (acetonitrile-water) to give β-anomer (91β) as white powder [2.05 g (yield 61.1%)].

Example 14

Synthesis of glucosylbetamethasone (*o*-toluoyl derivative) (Fig. 14)

1) Toluoylation of glucose 1 → 92

[0163] D-(+)-Glucose (1) (1.21 g) was dissolved in chloroform (24 ml), and to this solution were added *p*-toluoyl chloride (8.85 ml) and pyridine (5.49 ml) drop-wise at 0 - 5°C. While the reaction temperature was slowly raised to room temperature, the reaction mixture was stirred for 4 h. The reaction solution was poured into ice-water, and extracted with chloroform. The organic layer was washed successively with saturated solutions of copper sulfate, sodium bicarbonate, and sodium chloride. After the solution was dried over anhydrous magnesium sulfate, the solvent was evaporated from the solution *in vacuo*. The residue thus obtained was purified by silica gel column chromatography (toluene:ethyl acetate = 6:1) to give 92 as white powder [5.16 g (quant.)].

Compound 92

[0164]

$C_{46}H_{42}O_{11}$ MW = 770.881
^{1}H-NMR [500MHz, $CDCl_3$, Ref = 0.000ppm(TMS)]

δ ; 2.578, 2.561, 2.492, 2.439, 2.352
(15H, 5s, $CH_3C_6H_4CO$-)
6.877 (1H, d, J = 3.66, H-1)
8.061, 7.961, 7.887, 7.831, 7.790
(5H, 5d, J = 8.06, $CH_3C_6H_4CO$-)

2) Bromination of glucose (*o*-toluoyl derivative) 92 → 93

[0165] 92 (2.84 g) was dissolved in chloroform (13 ml), and to this solution was added hydrogen bromide-acetic acid solution (7.7 ml) at 0 - 5°C. While the reaction temperature was slowly raised to room temperature, the mixture was stirred for 3 h. After the unreacted bromine was removed with an argon stream, the solvent was distilled off *in vacuo*. The residue was dissolved in chloroform, and the solution was washed cold saturated sodium bicarbonate solution. After the chloroform solution was dried over anhydrous magnesium sulfate, the solvent was evaporated *in vacuo* to give 93 as pale yellow powder [2.44 g (yield 92.6%)].

Compound 93

[0166]

$C_{38}H_{35}O_9Br$ MW = 715.593
^{1}H-NMR [500MHz, $CDCl_3$, Ref = 0.000ppm(TMS)]

δ ; 2.611, 2.553, 2.451, 2.340
(12H, 4s, $CH_3C_6H_4CO$-)
6.890 (1H, d, J = 4.03, H-1)
8.002, 7.974, 7.912, 7.734
(4H, 4d, J = 8.06, $CH_3C_6H_4CO$-)

3) Synthesis of glucosylbetamethasone (*o*-toluoyl derivative)

93+86→94

[0167] Betamethasone (86) (350 mg) was dissolved in acetonitrile (23 ml), and to this solution were added molecular sieve 3A (460 mg) and silver triflate (437 mg). To this mixture was added, under an argon atmosphere and at 0 - 5°C, a bromide of glucose (*o*-toluoyl derivative) (93) (1.22 g) dissolved in acetonitrile (12 ml). While the reaction temperature was slowly raised to room temperature, the mixture was stirred for 6 h. To this mixture was further added silver triflate (437 mg), and the resulting mixture was stirred at room temperature for 17 h. The reaction solution was filtered, and the solvent was distilled off from the filtrate *in vacuo*. The residue was dissolved in chloroform, and washed with saturated sodium chloride solution. After the chloroform solution was dried over anhydrous magnesium sulfate, the solvent was evaporated *in vacuo*. The residue thus obtained was purified by silica gel column chromatography (hexane:ethyl acetate = 5:4) to give white powder (723.8 mg). This powder was further purified by HPLC using a reversed phase partition column chromatography (acetonitrile-water) to give 94β as white powder [450.4 mg (yield 49.2%)].

Compound 94β

[0168]

$C_{60}H_{63}O_{14}F$ MW = 1027.15
^{1}H-NMR [500MHz, $CDCl_3$, Ref = 0.000ppm(TMS)]

δ ; 2.574, 2.482, 2.436, 2.277 (12H, 4s, $CH_3C_6H_4CO$-)

4.119-4.081 (1H, m, H-5)
4.578 (2H, d, J = 4.39, H-6, 6')
5.043 (1H, d, J = 8.06, H-1)
5.542 (1H, dd, J = 9.53, H-2)
5.642 (1H, t, H-4)
5.898 (1H, t, H-3)
6.113 (1H, s, Bet-4)
6.319 (1H, d, Bet-1)
7.965, 7.840, 7.755
(4H, 3d, J = 6.96, $CH_3C_6\underline{H}_4CO$-)

FAB(+)MS calcd. 1026.42 ; 1049$(M+Na)^+$
MP : 124 - 127°C
IR ν_{max}^{KBr} cm^{-1} 1734(C = O position-20), 1665(C = O position-3)

Example 15

Synthesis of glucosylbetamethasone (*m*-toluoyl derivative) (Fig. 15)

1) *m*-Toluoylation of glucose 1 →95

[0169] D-(+)-Glucose (1) (1.26 g) was dissolved in chloroform (24 ml), and to this solution were added *m*-toluoyl chloride (9.20 ml) and pyridine (5.65 ml) at 0 - 5°C. While the reaction temperature was slowly raised to room temperature, the mixture was stirred for 3 h. The reaction solution was poured into ice-water, and extracted with chloroform. The organic layer was washed successively with saturated solutions of copper sulfate, sodium bicarbonate, and sodium chloride. After the chloroform solution was dried over anhydrous magnesium sulfate, the solvent was evaporated *in vacuo*. The residue thus obtained was purified by silica gel column chromatography (hexane:ethyl acetate = 5:1) to give 95 as white powder [5.49 g (quant.)].

Compound 95

[0170]

$C_{46}H_{42}O_{11}$ MW = 770.881
^{1}H-NMR [500MHz, $CDCl_3$, Ref = 0.000ppm(TMS)]

δ ; 2.463, 2.372, 2.328, 2.293, 2.248
(15H, 5s, $C\underline{H}_3C_6H_4CO$-)
6.834 (1H, d, J = 4.03, H-1)

2) Bromination of glucose (*m*-toluoyl derivative) (97) 95→96

[0171] (95) (2.64 mg) was dissolved in chloroform (12 ml), and to this solution was added hydrogen bromide-acetic acid solution (5.2 ml) at 0 - 5°C. While the reaction temperature was slowly raised to to room temperature, the mixture was stirred for 5 h. After the unreacted bromine was removed with an argon stream, the solvent was distilled off *in vacuo*. The residual material was dissolved in chloroform, and washed with cold saturated sodium bicarbonate solution. After the chloroform solution was dried over anhydrous magnesium sulfate, the solvent was evaporated in vacuo to give 96 as white powder [2.27 g (yield 92.5%)].

Compound 96

[0172]

$C_{38}H_{35}O_9Br$ MW = 715.593
^{1}H-NMR [500MHz, $CDCl_3$, Ref = 0.000ppm(TMS)]

δ ; 2.401, 2.353, 2.338, 2.290(12H, 4s, $C\underline{H}_3C_6H_4CO$-)
6.874 (1H, d, J = 4.03, H-1)

7.865, 7.799, 7.755, 7.684
(8H, 4d, J = 7.70, $CH_3C_6\underline{H_4}CO$-)

3) Synthesis of glucosylbetamethasone (*m*-toluoyl derivative) (97) 96+86→97

[0173] Betamethasone (86) (334 mg) was dissolved in acetonitrile (23 ml), and to this solution were added molecular sieve 3A (460 mg) and silver triflate (437 mg). To this mixture was added, under an argon atmosphere and at 0 - 5°C, a bromide of glucose (*m*-toluoyl derivative) (96) (1.22 mg) dissolved in acetonitrile (12 ml). While the reaction temperature was slowly raised to room temperature, the mixture was stirred for 3 h. To this mixture was further added silver triflate (437 mg), and the resulting mixture was stirred at room temperature overnight. The reaction solution was filtered, and the solvent was distilled off from the mother liquor *in vacuo*. The residual material was dissolved in chloroform, and the solution was washed with saturated sodium chloride solution. After the chloroform solution was dried over anhydrous magnesium sulfate, the solvent was evaporated *in vacuo*. The residue thus obtained was purified by silica gel column chromatography (hexane:ethyl acetate = 5:4) to give white powder (819 mg). A portion of this product (300 mg) was further purified by HPLC using a reversed phase partition column chromatography (acetonitrile-water) to give β-anomer (97β) as white powder [212.9 mg (yield 66.5%)].

Compound 97β

[0174]

$C_{60}H_{63}O_{14}F$ MW = 1027.15
^{1}H-NMR [500MHz, $CDCl_3$, Ref = 0.000ppm(TMS)]

δ ; 2.338, 2.317, 2.294, 2.272 (12H, 4s, $C\underline{H_3}C_6H_4CO$-)
4.133-4.096 (1H, m, H-5)
5.035 (1H, d, J = 8.06, H-1)
5.541 (1H, dd, J = 9.53, H-2)
5.656 (1H, t, H-4)
5.833 (1H, t, H-3)
6.135 (1H, s, Bet-4)
6.344 (1H, d, J = 9.89, Bet-1)
7.786, 7.738, 7.705, 7.642
(4H, 3d, J = 7.69, $CH_3C_6\underline{H_4}CO$-)

FAB(+)MS calcd. 1026.42 ; 1049(M+Na)$^+$
MP : 125 - 128°C
IR ν_{max}^{KBr} cm^{-1} 1735(C = O position-20), 1665(C = O position-3)

Example 16

Synthesis of glucosylbetamethasone (benzoyl derivative) (Fig. 16)

1)Benzoylation of glucose 1→98

[0175] D-(+)-Glucose (1) (1.30 g) was dissolved in chloroform (24 ml), and to this solution were added benzoyl chloride (8.3 ml) and pyridine (5.8 ml) drop-wise at 0 - 5°C. While the reaction temperature was slowly raised to room temperature, this mixture was stirred for 4 h. The reaction solution was poured into ice-water, and extracted with chloroform. The organic layer was washed successively with saturated solutions of copper sulfate, sodium bicarbonate, and sodium chloride. After the chloroform solution was dried over anhydrous magnesium sulfate, the solvent was evaporated *in vacuo*. The residue thus obtained was purified by silica gel column chromatography (hexane:ethyl acetate = 3:1) to give 98 as white powder [7.26 g (theoretical)].

Compound 98

[0176]

$C_{41}H_{32}O_{11}$ MW = 700.693

^{1}H-NMR [500MHz, $CDCl_3$, Ref = 0.000ppm(TMS)]

δ ; 5.683 (1H, dd, J = 10.26, H-2)
5.859 (1H, t, H-4)
6.319 (1H, t, H-3)
6.853 (1H, d, J = 4.03, H-1)
8.167, 8.026, 7.946, 7.874 (8H, 4d, J = 8.43, C_6H_5CO-)

2) Bromination of glucose (benzoyl derivative) 98→99

[0177] 98 (3.89 g) was dissolved in chloroform (19 ml), and to this solution was added hydrogen bromide-acetic acid solution (8.5 ml) at 0 - 5°C. While the reaction temperature was slowly raised to room temperature, the mixture was stirred for 4 h. After the unreacted bromine was removed with an argon stream, the solvent was evaporated from the reaction mixture *in vacuo*. The residue was dissolved in chloroform, and washed with cold saturated sodium bicarbonate solution. After the solution was dried over anhydrous magnesium sulfate, the solvent was distilled off *in vacuo* to give 99 as pale yellow powder [2.80 g (yield 76.4%)].

Compound 99

[0178]

$C_{34}H_{27}O_9Br$ MW = 659.485
^{1}H-NMR [500MHz, $CDCl_3$, Ref = 0.000ppm(TMS)]

δ ; 4.514 (1H, dd, J = 12.82, H-6)
4.667 (1H, dd, J = 4.77, H-6')
4.751-4.716 (1H, m, H-5)
5.328 (1H, dd, J = 9.89, H-2)
5.818 (1H, t, H-4)
6.263 (1H, t, H-3)
6.865 (1H, d, J = 4.03, H-1)
8.068, 8.002, 7.952, 7.874 (8H, 4d, J = 8.06, C_6H_5CO-)

3) Synthesis of glucosylbetamethasone (benzoyl derivative) 100

99+86→100

[0179] Betamethasone (86) (510 mg) was dissolved in acetonitrile (35 ml), and to this solution were added molecular sieve 3A (700 mg) and silver triflate (668 mg). To this mixture was added, under an argon atmosphere and at 0 - 5°C, a glucose bromide (benzoyl derivative) (99) (1.72 g) dissolved in acetonitrile (18 ml). While the reaction mixture was slowly raised to room temperature, the reaction mixture was stirred for 5 h. To this mixture was further added silver triflate (668 mg), and the resulting mixture was stirred at room temperature for 18 h. The reaction solution was filtered, and the solvent was distilled off from the mother liquor *in vacuo*. The residue thus obtained was dissolved in chloroform, and was washed with saturated sodium chloride solution. After the chloroform solution was dried over anhydrous magnesium sulfate, the solvent was evaporated *in vacuo*. The residue thus obtained was purified by silica gel column chromatography (hexane:ethyl acetate = 5:4) to give white powder (1.24 g), which was further purified by HPLC using a reversed phase partition chromatography (acetonitrile-water) to give β-anomer (100β) as white powder [813 mg (yield 64.4%)].

Compound 100β

[0180]

$C_{56}H_{55}O_{14}F$ MW = 971.04
^{1}H-NMR [500MHz, $CDCl_3$, Ref = 0.000ppm(TMS)]

δ ; 4.149-4.112 (1H, m, H-5) 5.064 (1H, d, J = 8.06, H-1)
5.562 (1H, dd, J = 9.53, H-2)

5.695 (1H, t, H-4)
5.917 (1H, t, H-3)
6.126 (1H, s, Bet-4)
6.339 (1H, d, Bet-1)
7.990, 7.947, 7.926, 7.832 (8H, 4d, J = 8.43, $C_6\underline{H_5}CO$-)

FAB(+)MS calcd. 970.36 ; 993 $(M+Na)^+$
MP : 142 - 145°C
IR ν_{max}^{KBr} cm^{-1} 1734(C = O position-20), 1665(C = O position-3)

Example 17

Synthesis of gulcosylbetamethasone (benzyl derivative) (Fig. 17)

1) S-Methylation of glucose 8 →101

[0181] β-D-Glucose-penta-O-acetate (8) (5 g) and tributyltin methylsulfide (6.5 g) were suspended in dichloroethane (40 ml), and to this suspension was added, under ice-cooling, tin(IV) chloride (1.94 ml). The resulting mixture was stirred at 0°C for 5 h. After the reaction mixture was-diluted with chloroform, a potassium fluoride solution was added to the above mixture, and stirred at room temperature. The reaction solution was filtered through celite, and the mother liquor was washed successively with saturated sodium bicarbonate solution, water, and saturated sodium chloride solution. After the organic layer was dried over anhydrous magnesium sulfate, the solvent was distilled off from the solution *in vacuo*. The residual material thus obtained was purified by silica gel column chromatography (hexane:ethyl acetate = 3:2) to give 101 as white powder [4.5 g (yield 93.2%)].

Compound 101

[0182]

$C_{15}H_{22}O_9S$ MW = 378.39
^{1}H-NMR [500MHz, $CDCl_3$, Ref =0.000ppm(TMS)]

δ ; 2.086, 2.069, 2.030, 2.013 (12H, 4s, $C\underline{H_3}COO$-)
2.173 (3H, s, $C\underline{H_3}S$-)
3.754-3.720 (1H, m, H-5)
4.151 (1H, dd, J = 12.46, H-6)
4.256 (1H, dd, J = 5.13, H-6')
4.399 (1H, d, J = 9.90, H-1)
5.107-5.056 (2H, m, H-2, H-4)
5.235 (1H, t, J = 9.52, H-3)

2) Benzylation of glucose (S-methyl derivative) 101 →102

[0183] Glucose (S-methyl derivative) (101) (400 mg) was dissolved in methanol (6 ml), and to this solution was added 1 M sodium methoxide (0.5 ml) at 0 - 5°C. The mixture was stirred at room temperature for 5 h. After the solvent was distilled off from the reaction mixture *in vacuo*, the residual material was dissolved in DMF (9 ml), and to this solution were added benzyl bromide (1.45 g) at 0°C,followed by sodium hydride (0.4 mg). The resulting mixture was stirred for 3 h, while it was allowed to warm up slowly to room temperature. Then, to this reaction mixture gas added methanol under ice-cooling, and the resulting mixture was evaporated *in vacuo*. To the residue thus obtained was added diethyl ether, and the solution was washed with saturated sodium chloride solution. After the solution was dried over anhydrous magnesium sulfate, the solvent was distilled off *in vacuo*. The residual material thus obtained was purified by silica gel column chromatography (hexane:ethyl acetate = 7:1) to give 102 as white powder [445.2 mg (yield 73.8%)].

Compound 102

[0184]

$C_{35}H_{38}O_5S$ MW = 570.75

^{1}H-NMR [500MHz, $CDCl_3$, Ref = 0.000ppm(TMS)]

δ ; 2.244 (3H, s, CH_3S-)
4.362 (1H, d, J = 9.52, H-1)

3) Synthesis of glucosylbetamethasone (benzyl derivative) 103 102 + 86→103

[0185] Betamethasone (86) (114 mg) and glucose (O-benzyl, SMe-derivative) (102) (200 mg) were dissolved in chloroform (6 ml), and to this solution were added molecular sieve 4A (80 mg), followed by methyl triflate (75 μl) at -20°C. While the reaction temperature was slowly raised to room temperature, the mixture was stirred for 5 h. The reaction solution was basified by the addition of triethylamine, filtered, and the solvent was distilled off from the mother liquor *in vacuo*. The residue was then diluted with chloroform, and the resulting solution was washed with saturated solutions of sodium bicarbonate and sodium chloride. After the solution was dried over anhydrous magnesium sulfate, the solvent was distilled off *in vacuo*. Residual material thus obtained was purified by silica gel column chromatography (hexane:ethyl acetate = 5:4) to give 103 (mixture of α-, β-anomers, α:β = 3:1) as white powder [200 mg (yield 75.4%)].

Compound 103

[0186]

$C_{56}H_{63}O_{10}F$ MW = 915.11
^{1}H-NMR [500MHz, $CDCl_3$, Ref = 0.000ppm(TMS)]

δ ; 3.492 (0.25H, dd, H-2, β)
3.598 (0.75H, dd, H-2, α)
4.504 (0.25H, d, J = 7.70, H-1, β)
4.823 (0.75H, d, J = 4.03, H-1, α)
6.110 (0.25H, s, Bet-4, β)
6.143 (0.75H, s, Bet-4, α)
6.310 (0.25H, s, Bet-1, β)
6.338 (0.75H, s, Bet-1, α)

FAB(+)MS calcd., 914.44 ; 915$(M+H)^+$
MP : 80 - 83°C
IR ν_{max}^{KBr} cm^{-1} 1725(C = O position-20), 1663(C = O position-3)

Examples 18 - 23

Syntheses of glucosyldifluorosteroids (Figs. 18 - 23)

1) Synthesis of glucosyldiflupredonate (*p*-toluoyl derivative) 105

3 + 104 → 105

[0187] Diflupredonate hydrolysate (104) (315 mg) was dissolved in acetonitrile (18 ml), and to this solution were added molecular sieve 3A (439 mg) and silver triflate (409 mg). To this mixture was added, under an argon atmosphere and at 0 - 5°C, a glucose bromide (3) (1.14 g) dissolved in acetonitrile (18 ml). While the reaction temperature was raised slowly to room temperature, the resulting mixture was stirred for 2 h. To this mixture was further added silver triflate (409 mg), and the resulting mixture was stirred at room temperature for 18 h. After the reaction solution was filtered, the solvent of the mother liquor was evaporated *in vacuo*. The residue was dissolved in chloroform, and washed with saturated sodium chloride solution. After the solution was dried over anhydrous magnesium sulfate, the solvent was evaporated *in vacuo*. The residue thus obtained was purified by silica gel column chromatography (hexane:ethyl acetate = 2:1) to give white powder (870 mg). This product was further purified by HPLC using a reversed phase partition column (acetonitrile-water) to give β-anomer (105β) as white powder [641 mg (yield 78.2%)].

Compound 105β

[0188]

$C_{59}H_{60}O_{14}F_2$ MW = 1031.11
^{1}H-NMR [500MHz, $CDCl_3$, Ref = 0.000ppm(TMS)]

δ : 2.420, 2.371, 2.340, 2.296(12H, 4s, $CH_3C_6H_4O$-)
4.085-4.047 (1H, m, H-5)
4.561 (1H, dd, H-6)
4.792 (1H, dd, H-6')
4.889 (1H, d, J = 8.06, H-1)
5.454 (1H, dd, H-2)
5.633 (1H, t, H-3)
5.913 (1H, t, H-4)
7.869, 7.849, 7.828, 7.740
(8H, 4d, J = 8.43, $CH_3C_6H_4O$-)

FAB(+)MS calcd. 1030.4 ; 1031$(M+H)^+$, 1013$(M-H_2O)^+$
MP : 152 - 155°C
IR ν_{max}^{KBr} cm^{-1} 1733(C = O position-20), 1630(C = O position-3)

2) Synthesis of glucosyldiflorasone (*p*-toluoyl derivative) 107

3 + 106 → 107

[0189] Hydrolysate of diflorasone (*p*-toluoyl derivative) (106) (206 mg) and a glucose bromide (3) (720 mg) were dissolved in a mixture of acetonitrile (3 ml) and cyanoethane (5 ml). To this solution was added molecular sieve 3A (1.0 g), and the mixture was stirred at room temperature for 3 h. This mixture was cooled to 0°C, and to the cooled mixture was added silver triflate (262 mg) dissolved in cyanoethane (1 ml). The resulting mixture was stirred for 20 h, while the reaction temperature was slowly raised to room temperature under an argon atmosphere. The reaction solution was diluted with chloroform, filtered through celite, and the mother liquor was washed with saturated sodium bicarbonate solution and then with saturated sodium chloride solution. After the chloroform solution was dried over anhydrous magnesium sulfate, the solvent was distilled off *in vacuo*. The residue thus obtained was purified by silica gel column chromatography (toluene:ethyl acetate = 7:3) to give white powder (317 mg). This product was further purified by HPLC using reversed phase partition column (acetonitrile-water) to give β-anomer (107β) as white powder [231 mg (yield 44.4%)].

Compound 107β

[0190]

$C_{60}H_{62}O_{14}F_2$ MW = 1045.14
^{1}H-NMR [500MHz, $CDCl_3$, Ref = 0.000ppm(TMS)]

δ : 2.387, 2.354, 2.351, 2.291 (12H, 4s, $CH_3C_6H_4O$-)
4.120-4.084 (1H, m, H-5)
4.278 (1H, t, H-6)
4.582 (1H, t, H-6')
4.999 (1H, d, J = 8.06, H-1)
5.516 (1H, dd, H-2)
5.644 (1H, t, H-4)
5.873 (1H, t, H-3)
6.358 (1H, d, Diflora-1)
6.427 (1H, s, Diflora-4)
7.860, 7.830, 7.786, 7.717
(8H, 4d, J = 8.06, $CH_3C_6H_4O$-)

FAB(+)MS calcd. 1044.41 ; 1045(M+H)$^+$, 1067(M+Na)$^+$,
IR ν_{max}^{KBr} cm^{-1} 1733(C = O position-20), 1671(C = O position-3)

3) Glucosyldiflucortolone (*p*-toluoyl derivative) 109

3 + 108 → 109

[0191] Hydrolysate of diflucortolone (108) (200 mg) was dissolved in acetonitrile (2 ml), and to this solution was added molecular sieve 3A (2 g). The mixture was stirred for 30 min. To this mixture were added, under an argon atmosphere and at 0 - 5°C, a glucose bromide (3) (725 mg) dissolved in acetonitrile (1 ml) and silver triflate (261 mg), and the resulting mixture was stirred for 2.5 h, while the reaction temperature was raised slowly to room temperature. After the reaction solution was filtered, the solvent was distilled off from the mother liquor *in vacuo*, and the residue was dissolved in ethyl acetate. The solution was washed with saturated sodium bicarbonate solution, then with saturated sodium chloride solution, and dried over anhydrous magnesium sulfate. After the solvent was distilled off *in vacuo*, the residue thus obtained was purified by silica gel column chromatography (toluene:ethyl acetate = 4:1) to give white powder (379 mg). A 370-mg portion of the product was further purified by HPLC using a reversed phase partition column (acetonitrile-water) to give β-anomer (109β) as white powder [289 mg (yield 55.1%)].

Compound 109β

[0192]

$C_{60}H_{62}O_{13}F_2$ MW = 1029.14
^{1}H-NMR [500MHz, $CDCl_3$, Ref = 0.000ppm(TMS)]

δ : 2.421, 2.364, 2.341, 2.293 (12H, 4s, $CH_3C_6H_4O$-)
4.070-4.033 (1H, m, H-5)
4.972 (1H, d, J = 8.06, H-1)
5.478 (1H, dd, H-2)
5.639 (1H, t, H-3)
5.884 (1H, t, H-4)
6.370 (1H, d, Difluco-1)
6.437 (1H, s, Difluco-4)
7.872, 7.831, 7.822, 7.729
(8H, 4d, J = 8.06, $CH_3C_6H_4O$-)

FAB(+)MS calcd. 1028.4 ; 1029(M+H)$^+$
MP : 144 - 147°C
IR ν_{max}^{KBr} cm^{-1} 1734(C = O position-20), 1672(C = O position-3)

4) Synthesis of glucosyldiflucortolone (benzoyl derivative)

99+108 → 110α+110β

[0193] Hydrolysate of diflucortolone (108) [299.1 mg (0.758 mmol)] was dissolved in acetonitrile (20 ml), and to this solution were added molecular sieve 3A (about 700 mg) and silver triflate [390.6 mg (1.52 mmol)]. The mixture was stirred for 1 h. To this mixture was added, under an argon atmosphere and at 0°C,a benzoylglucose bromide (99) [1.0 g (1.52 mmol)] dissolved in acetonitrile (10 ml). While the reaction temperature was slowly raised to room temperature, the mixture was stirred for 2 h. To this mixture was further added silver triflate (390.6 mg), and the resulting mixture was stirred at room temperature for 14 h. To this mixture was further added silver triflate (390.6 mg), and the resulting mixture was stirred at room temperature for 4 h. After the reaction solution was filtered, the solvent was distilled off from the filtrate *in vacuo*. The residue thus obtained was dissolved in chloroform, and the solution was washed with saturated sodium chloride solution. After the solution was dried over anhydrous magnesium sulfate, the solvent was distilled off *in vacuo*. The residue thus obtained was purified by silica gel column chromatography (ethyl acetate:hexane = 2:3 → 4:5) to give fractions containing the desired product (360.2 mg). This product was further purified by HPLC using a reversed phase partition column (water-acetonitrile) to give α-anomer (110α) [19.9 mg (yield 2.7%)] and β-anomer (110β) [249.9 mg (yield 33.9%)], respectively, both as white powder.

Compound 110α

[0194]

$C_{56}H_{54}F_2O_{13}$ MW = 972.35
MP : 135 - 138°C
FAB(+)MS ; 955$(M-H_2O)^+$, 973$(M+H)^+$, 995$(M+Na)^+$
IR ν_{max}^{KBr} cm^{-1} : 3448(O-H), 1731(COPh), 1671(C=O 3-position), 1616 and 1603(C=C)
^{1}H-NMR [500MHz, $CDCl_3$, Ref = 0.000ppm(TMS)]

δ ; 7.169(1H, d, $J_{2.1}$ = 10.3, H-2)
6.437(1H, d, $J_{4.1}$ = 1.8, H-4)
6.408(1H, dd, H-1)
6.250(1H, t, $J_{3.2}$ = 9.9, $J_{3.4}$ = 9.9, H-3_{Glc})
5.780(1H, t, $J_{4.5}$ = 10.3, H-4_{Glc})
5.338(1H, d, $J_{1.2}$ = 3.7, H-1_{Glc})
5.223(1H, dd, H-2_{Glc})
4.917(1H, dd, $H_{6.5}$ = 3.3, $J_{6.6'}$= 12.5, H-6_{Glc})
4.657(1H, ddd, $J_{6.6'}$= 2.6, H-5_{Glc})
4.296(1H, dd, H-$6'_{Glc}$)
4.249(1H, d, J_{gem} = 17.6, H-21)
4.231(1H, d, H-21')
1.553(3H, s, H-19)
1.077(3H, s, H-18)
0.968(3H, d, $J_{16CH3.16}$ = 7.0, 16-CH_3)

Compound 110β

[0195]

$C_{56}H_{54}F_2O_{13}$ MW = 972.35
MP : 140 - 145°C
FAB(+)MS ; 955$(M-H_2O)^+$, 973$(M+H)^+$, 995$(M+Na)^+$
IR ν_{max}^{KBr} cm^{-1} : 3440(O-H), 1731(COPh), 1671(C=O position-3), 1604(C=C)
^{1}H-NMR [500MHz, $CDCl_3$, Ref = 0.000ppm(TMS)]

δ ; 7.115(1H, dd, $J_{2.1}$ = 10.3, H-2)
6.438(1H, d, $H_{4.1}$ = 1.8, H-4)
6.374(1H, dd, H-1)
5.927(1H, t, $J_{3.2}$ = 9.9, $J_{3.4}$ = 9.9, H-3_{Glc})
5.704(1H, t, $J_{4.5}$ = 9.9, H-4_{Glc})
5.519(1H, dd, $J_{2.1}$ = 7.7, H-2_{Glc})
5.038(1H, d, H-1_{Glc})
4.691(2H, dd, $J_{6.5}$ = 4.0; H-6_{Glc})
4.268(1H, d, J_{gem} = 16.9, H-21)
4.133(1H, d, H-21')
4.084(1H, td, H-5_{Glc})
1.558(3H, s, H-19)
0.900(3H, s, H-18)
0.821(3H, d, $J_{16CH3.16}$ = 7.0, 16-CH_3)

5) Synthesis of glucosyldiflucortolone (*p*-chlorobenzoyl derivative) 112

109 →111 →112

[0196] Glucosyldiflucortolone (*p*-toluoyl derivative; 109) (1.34 g) was dissolved in chloroform (40 ml), and to this solution was added, under ice-cooling, 1 M sodium methoxide (1.04 ml). While the reaction temperature was slowly raised to room temperature, the mixture was stirred for 1 h. To this reaction solution was added methanol (30 ml), and

the resulting mixture was stirred for 3 h. The reaction solution was applied to a gel filtration column of LH-20, and eluted with methanol. The solvent of fractions containing product was distilled off *in vacuo* and the residue thus obtained was recrystallized from methanol to give glucosyldiflucortolone (deprotected derivative; 111) (408.4 mg). To a portion of the product (102.5 mg) were added, at 0 - 5°C, *p*-chlorobenzoyl chloride (190 µl) and pyridine (0.9 ml), and, while the reaction temperature was slowly raised to room temperature, the mixture was stirred for 6 h. Then, to the mixture was added methanol (1 ml), and the resulting mixture was stirred at room temperature for 30 min. The reaction solution was applied to a gel filtration column of LH-20, and eluted with methanol. After the solvent of fractions containing product was distilled off *in vacuo*, the residue thus obtained was purified by silica gel column chromatography (toluene:ethyl acetate = 4:1) to give 112 as white powder [152.2 mg (yield 42.0%) (109 → 112 in two steps)].

Compound 111

[0197]

$C_{28}H_{38}O_9F_2$ MW = 556.60
^{1}H-NMR [500MHz, DMSO, Ref = 0.000ppm(TMS)]

δ : 3.079 (1H, t, J = 5.49, H-6')
3.118 (1H, t, J = 8.43, H-2)
3.272 (1H, d, J = 7.79, H-3)
3.439 (1H, dd, J = 11.36, H-5)
4.161 (1H, d, J = 8.06, H-1)
6.107 (1H, s, Difluco-4)
6.292 (1H, d, Difluco-1)

FAB(+)MS calcd. 556.2; 557(M+H)$^+$
MP : 162 - 164°C
IR ν_{max}^{KBr} cm^{-1} : 1716(C = O position-20), 1630(C=O position-3)

Compound 112

[0198]

$C_{56}H_{50}O_{13}Cl_4F_2$ MW = 1110.81
^{1}H-NMR [500MHz, $CDCl_3$, Ref = 0.000ppm(TMS)]

δ : 4.057 (1H, ddd, J = 4.03, H-5)
4.605 (1H, dd, J = 4.03, H-6')
4.693 (1H, dd, J = 12.45, H-6)
5.046 (1H, d, J = 7.70, H-1)
5.471 (1H, dd, J = 9.53, H-2)
5.654 (1H, t, J = 9.86, H-4)
5.843 (1H, t, J = 9.86, H-3)
7.286, 7.349, 7.352, 7.411
(8H, 4d, J = 8.79, ClC_6H_4CO-)
7.762, 7.838, 7.890, 7.902
(8H, 4d, J = 8.79, ClC_6H_4CO-)

FAB(+)MS calcd. 1108.2 ; 1109(M+H)$^+$
MP : 147 - 149°C
IR ν_{max}^{KBr} cm^{-1} : 1738(C = O position-20), 1634(C =O position-3)

6) Synthesis of glucosyldiflucortolone (acetyl derivative) 113

109 →113

[0199] Glucosyldiflucortolone (*p*-toluoyl derivative; 109) (1.55 g) was dissolved in chloroform (50 ml), and to this solution was added, under ice-cooling, 1 M sodium methoxide (1.21 ml). While the reaction temperature was slowly

raised to room temperature, the mixture was stirred for 1 h. Then, to the reaction solution was added methanol (40 ml), and the mixture was stirred at room temperature for 3 h. After the solvent was distilled off *in vacuo*, acetic anhydride (8.0 ml) and pyridine (1.8 ml) were added to the residue under ice-cooling, and the resulting mixture was slowly raised to room temperature, the mixture was stirred for 2 h. To this mixture was further added acetic anhydride (2.6 ml) and pyridine (0.6 ml), the mixture was stirred for 3 h. The reaction solution was poured into ice-water, extracted with chloroform, and the chloroform solution was washed successively with saturated sodium bicarbonate solution, 5% copper sulfate solution, and saturated sodium chloride solution. The chloroform solution was dried over anhydrous magnesium sulfate, and then the solvent was evaporated *in vacuo*. The residue thus obtained was recrystallized from ethyl acetate to give 113 as white powder [668 mg (yield 61.2%)].

Compound 113

[0200]

$C_{36}H_{46}O_{13}F_2$ MW = 724.75
^{1}H-NMR [500MHz, $CDCl_3$, Ref = 0.000ppm(TMS)]

δ : 2.117, 2.069, 2.051, 2.019 (12H, 4s, CH_3COO-)
3.663 (1H, ddd, J = 5.13, H-5)
4.198 (1H, dd, J = 2.93, H-6')
4.389 (1H, dd, J = 12.46, H-6)
4.733 (1H, d, J = 8.06, H-1)
5.005 (1H, dd, J = 9.52, H-2)
5.007 (1H, t, J = 9.52, H-4)
5.235 (1H, t, J = 9.52, H-3)
6.383 (1H, d, Difluco-1)
6.429 (1H, s, Difluco-4)

FAB(+)MS calcd. 724.3 ; 725$(M+H)^+$
MP : 233 - 235°C
IR ν_{max}^{KBr} cm^{-1} 1760(C = O position-20), 1671(C = O position-3)

Example 24

Synthesis of glucosyldexamethasone (acetyl derivative) (Fig. 24)

1) Glucosyldexamethasone (acetyl derivative) 5β → 114β

[0201] A deprotected derivative (5β) of glucosyldexamethasone (β-anomer) (278 mg) was dissolved in acetic anhydride (1.75 ml), and to this solution was added, under ice-cooling, pyridine (0.40 ml). While the reaction temperature was slowly raised to room temperature, the mixture was stirred for 1 h. The reaction solution was poured into ice-water, and extracted with chloroform. The chloroform solution was washed successively with saturated sodium bicarbonate solution, 5% copper sulfate solution, and saturated sodium chloride solution. After the chloroform solution was dried over anhydrous magnesium sulfate, the solvent was evaporated *in vacuo*. The residue thus obtained was purified by silica gel column chromatography (hexane:ethyl acetate = 1:2) to give white powder (198 mg). This product was further purified by HPLC using a reversed phase partition column (acetonitrile-water) to give 114β as white powder [147 mg (yield 40.5%)].

Compound 114β

[0202]

$C_{36}H_{47}O_{14}F$ MW = 722.76
^{1}H-NMR [500MHz, $CDCl_3$, Ref = 0.000ppm(TMS)]

δ : 2.119, 2.094, 2.047, 2.022 (12H, 4s, CH_3COO-)
3.690 -3.654 (1H, m, H-5)
4.219 (1H, dd, J = 12.09, 3.29, H-6)

4.336 (1H, dd, J = 4.77, H-6')
4.746 (1H, d, J = 8.06, H-1)
5.027 (1H, dd, J = 9.15, H-2)
5.087 (1H, t, H-4)
5.245 (1H, t, H-3)
6.121 (1H, s, Dex-4)
6.347 (1H, d, Dex-1)

FAB(+)MS calcd. 722.29 ; 723$(M+H)^+$, 705$(M-H_2O)^+$
MP : 125 - 128°C
IR ν_{max}^{KBr} cm^{-1} 1758(C = O position-20), 1666(C = O position-3)

Example 25

Synthesis of galactosyldexamethasone (acetyl derivative) (Fig. 25)

1) Synthesis of galactosyldexamethasone (acetyl derivative) 115β 14β → 115β

[0203] Galactosyldexamethasone (*p*-toluoyl derivative; 14β) (762 mg) was dissolved in chloroform (25 ml), and to this solution was added, under ice-cooling, 1 M sodium methoxide (592 µl). While the reaction temperature was slowly raised to room temperature, the mixture was stirred for 2 h. To this reaction solution was added methanol (25 ml), and the mixture was stirred at room temperature for 1 h. After the solvent was evaporated *in vacuo*, acetic anhydride (3.90 ml) and pyridine (0.90 ml) were added to the residue under ice-cooling. While the reaction temperature was raised slowly to room temperature, the mixture was stirred for 12 h. To this mixture were further added acetic anhydride (1.30 ml) and pyridine (0.30 ml), and the resulting mixture was stirred at room temperature for 4 h. The reaction solution was poured onto ice-water, and extracted with chloroform. The chloroform solution was washed successively with saturated sodium bicarbonate solution, 5% copper sulfate solution and saturated sodium chloride solution. After the solvent wad distilled off *in vacuo*, the residue thus obtained was purified by silica gel column chromatography (hexane:ethyl acetate = 2:3) to give white powder (462 mg). This product was further purified by HPLC using a reversed phase partition column (acetonitrile-water) to give 115β as white powder [171 mg (yield 31.9%)].

Compound 115β

[0204]

$C_{36}H_{47}O_{14}F$ MW = 722.76
^{1}H-NMR [500MHz, $CDCl_3$, Ref = 0.000ppm(TMS)]

δ : 2.190, 2.132, 2.101, 2.002 (12H, 4s, CH_3COO-)
4.454 (1H, dd, H-6')
4.575 (1H, d, J = 8.06, H-1)
4.621.(1H, dd, H-2)
5.032 (1H, t, H-3)
5.239 (1H, t, H-2)
5.392 (1H, d, H-4)
6.115 (1H, s, Dex-4)
6.331 (1H, d, Dex-1)

FAB(+)MS calcd. 722.29 ; 723$(M+H)^+$, 705$(M-H_2O)^+$
MP : 138 - 141°C
IR ν_{max}^{KBr} cm^{-1} 1753(C = O position-20), 1666(C = O position-3)

Example 26

Synthesis of glucosylbetamethasone valerate (*m*-toluoyl derivative) (Fig. 26)

1) Synthesis of glucosylbetamethasone valerate (*m*-toluoyl derivative) 117

96+116 → 117

[0205] Betamethasone valerate (116) (405 mg) was dissolved in acetonitrile (23 ml), and to this solution were added molecular sieve 3A (460 mg) and silver triflate (437 mg). To this mixture was added, under an argon atmosphere and at 0 - 5°C, a glucose bromide (*m*-toluoyl derivative (96) (1.22 g). While the reaction temperature was raised slowly to room temperature, the mixture was stirred for 5 h. After the reaction solution was filtered, the solvent of the mother liquor was evaporated *in vacuo*. The residue was dissolved in chloroform, and washed with saturated sodium chloride solution. After the solution was dried over anhydrous magnesium sulfate, the solvent was evaporated *in vacuo*. The residue thus obtained was purified by silica gel column chromatography (hexane:ethyl acetate = 5:4) to give white powder (779 mg). This product was further purified by HPLC using a reversed phase partition column (acetonitrile-water) to give β-anomer (117β) [407 mg (yield 43.1%)] and α-anomer (117α) [59 mg (yield 6.3%)], respectively, both as white powder.

Compound 117β

[0206]

$C_{65}H_{71}O_{15}F$ MW = 1111.2
^{1}H-NMR [500MHz, $CDCl_3$, Ref = 0.000ppm(TMS)]

δ : 2.352, 2.307, 2.290, 2.277 (12H, 4s, $CH_3C_6H_4O$-)
4.088-4.051 (1H, m, H-5)
4.353 (1H, d, J = 9.16, H-6)
4.663 (1H, d, J = 4.76, H-6')
5.135 (1H, d, J = 8.06, H-1)
5.481 (1H, dd, H-2)
5.675 (1H, t, H-4)
5.869 (1H, t, H-3)
6.181 (1H, s, Bet-4)
6.400 (1H, d, Bet-1)
7.800, 7.712, 7.475 (8H, 3d, J = 7.69, $CH_3C_6H_4O$-)

FAB(+)MS calcd. 1110.48 ; 1111$(M+H)^+$,
1094$(M-H_2O)^+$
MP : 113 - 115°C
IR ν_{max}^{KBr} cm^{-1} 1734(C = O position-20), 1668(C = O position-3)

Compound 117α

[0207]

$C_{65}H_{71}O_{15}F$ MW = 1111.2
^{1}H-NMR [500MHz, $CDCl_3$, Ref = 0.000ppm(TMS)]

δ : 2.386, 2.339, 2.333, 2.284 (12H, 4s, $CH_3C_6H_4O$-)
4.088-4.051 (1H, m, H-5)
5.330 (1H, d, J = 3.67, H-1)
6.162 (1H, s, Bet-4)
6.385 (1H, d, Bet-1)
7.831, 7.772, 7.676 (8H, 3d, J = 8.06, $CH_3C_6H_4O$-)

FAB(+)MS calcd. 1110.48 ; 1111$(M+H)^+$,
1094$(M-H_2O)^+$

MP : 105 - 108°C
IR ν_{max}^{KBr} cm^{-1} 1732(C = O position-20), 1668(C = O position-3)

Synthesis of β-rhamnosyldexamethasone (Fig. 27)

1) Synthesis of a protected (acetyl) derivative of rhamonosyldexamethasone 119 (glucosylation)

[0208] Dexamethasone (6) (1.10 g) and rhamnose (o-acetyl, S-methyl derivative) 118 (1.12 g) were dissolved in tetrahydrofuran (10 ml), and this solution was added to molecular sieve 4A (1.2 g) contained in a brown reaction vessel. To this mixture was added, at -10°C, methyl triflate (2 ml), and, while the reaction temperature was slowly raised to room temperature, the mixture was stirred for 4 h. The reaction solution was diluted with ethyl acetate (10 ml) and neutralized by the addition of triethylamine. The mixture was filtered, diluted with ethyl acetate (300 ml), and washed with saturated sodium bicarbonate solution followed by saturated sodium chloride solution. After the solution was dried over anhydrous magnesium sulfate, the solvent was evaporated *in vacuo*. The residue thus obtained was purified by silica gel column chromatography (toluene:acetone = 1:1) to give 119β as white powder [312.5 mg (yield 16.8%)].

Compound 119β

[0209]

$C_{34}H_{45}FO_{12}$ MW = 664.72
Rf = 0.62 (silica gel TLC, $CHCl_3$: methanol = 20 : 1)
^{1}H-NMR [500MHz, $CDCl_3$, Ref = 0.000ppm(TMS)]

δ ; 7.213 (1H, d, Dexa-H-2, $J_{2.1}$ = 10.3)
6.336 (1H, dd, Dexa-H-1, $J_{1.4}$ = 1.5)
6.115 (1H, d, Dexa-H-4)
5.376 (1H, dd, H-2, $J_{2.3}$ = 3.3, $J_{2.1}$ = 1.8)
5.321 (1H, dd, H-3, $J_{3.4}$ = 9.9)
5.088 (1H, dd, H-4, $J_{4.5}$ = 9.9)
4.785 (1H, d, H-1)
4.511 (1H, d, Dexa-H-21, J_{gem} = 16.5)
4.418 (1H, d, Dexa-H-21')
4.380 (1H, m, Dexa-H-11)
4.014 (1H, dq, H-5, $J_{5.6}$ = 6.2)
3.118 (1H, m, Dexa-H-16)
2.617 (1H, m, Dexa-H-6)
2.157, 2.057, 2.003 (3H x 3, each s, OAc x 3)
1.548 (3H, s, Dexa-H-19)
1.218 (3H, d, H-7')
1.055 (3H, s, Dexa-H-18)
0.910 (3H, d, Dexa-16CH_3, $J_{16CH3.16}$ = 7.3)

FAB(+)MS ; 665$(M+H)^+$
MP : 137 - 139°C
IR ν_{max}^{KBr} cm^{-1} 3430(O-H), 1752(C = O), 1668(C = O)

2) Synthesis of a deprotected derivative of rhamnosyldexamethasone (synthesis of 119β→120β)

[0210] A protected derivative of rhamnosyldexamethasone (119β) (103.4 mg) was dissolved in methanol (1 ml), and to this solution was added 1 M sodium methoxide (40 μl). The mixture was stirred at room temperature for 1 h. The reaction solution was applied to a gel filtration column of LH-20, and eluted with methanol. The solvent of fractions containing product was distilled off *in vacuo* to give 120β as white powder [55.4 mg (yield 64%)].

Compound 120β

[0211]

$C_{28}H_{39}FO_9$ MW = 538.61
Rf = 0.67(silica gel TLC, $CHCl_3$: methanol = 1 : 1)
^{1}H-NMR [500MHz, CD_3OD, Ref = 0.000ppm(TMS)]

δ ; 7.403 (1H, d, Dexa-H-2, $J_{2.1}$ = 10.3)
6.286 (1H, dd, Dexa-H-1, $J_{1.4}$ = 1.8)
6.115 (1H, d, Dexa-H-4)
4.682 (1H, d, H-1, $J_{1.2}$ = 1.5)
4.649 (1H, d, Dexa-H-21, J_{gem} = 18.3)
4.412 (1H, d, Dexa-H-21')
4.259 (1H, m, Dexa-H-11)
3.951 (1H, dd, H-2, $J_{2.3}$ = 3.3)
3.698 (1H, dd, H-3, $J_{3.4}$ = 9.5)
3.596 (1H, dq, H-5, $J_{5.4}$= 9.5, $J_{5.6}$ = 6.2)
3.383 (1H, dd, H-4)
3.062 (1H, m, Dexa-H-16)
2.713 (1H, m, Dexa-H-6)
2.480 (1H, m, Dexa-H-6')
2.317 (1H, m, Dexa-H-12)
2.222 (1H, m, Dexa-H-14)
1.876 (1H, m, Dexa-H-7)
1.727 (1H, m, Dexa-H-15)
1.580 (3H, s, Dexa-H-19)
1.265 (3H, d, H-6)
1.002 (3H, s, Dexa-H-18)
0.855 (3H, d, Dexa-16CH_3, $J_{16CH3.16}$ = 6.9)

FAB(+)MS ; 539$(M+H)^+$
MP : 144 - 146°C (decomp.)
IR ν_{max}^{KBr} cm^{-1} 3418(O-H), 1719(C = O), 1663(C = O)

Claims

1. Glycosides of steroid compounds as the aglycon, wherein:

   the 21-position of said steroid compounds is substituted with simple sugars or acylated derivatives of said simple sugars,

   the hydroxyl groups of said simple sugars or said acylated simple sugars are protected with toluoyl, benzoyl, p-chlorobenzoyl, or arylalkyl groups, and

   said steroid compounds consist of dexamethasone, betamethasone, the dideacyl derivative of diflupredonate, diflurasone, diflucortolone or betamethasone valerate.

2. Compounds as defined in claim 1, for use as an anti-inflammatory agent.

3. Glycosides of anti-inflammatory steroid compounds as the aglycon for use as an anti-inflammatory agent, wherein:

   the 21-position of said steroid compounds is substituted with simple sugars or acylated derivatives of said simple sugars, and

   the hydroxyl groups of said simple sugars or said acylated simple sugars are protected with toluoyl, benzoyl, p-chlorobenzoyl, or arylalkyl groups.

Patentansprüche

1. Glykoside von Steroidverbindungen als dem Aglykon, wobei:

   die 21-Stellung der Steroidverbindungen mit einfachen Zuckern oder acylierten Derivaten der einfachen Zukker substituiert ist,

   die Hydroxylgruppen der einfachen Zucker oder der acylierten einfachen Zucker mit Toluoyl-, Benzoyl-, p-Chlorbenzoyl- oder Arylalkylgruppen geschützt sind, und

   die Steroidverbindungen aus Dexamethason, Betamethason den Didesacylderivaten von Diflupredonat, Diflurason, Diflucortolon oder Betamethasonvalerat bestehen.

2. Verbindungen nach Anspruch 1 zur Verwendung als entzündungshemmendes Mittel.

3. Glykoside von entzündungshemmenden Steroidverbindungen als dem Aglykon zur Verwendung als entzündungshemmende, Mittel, wobei:

   die 21-Stellung der Steroldverbindungen mit einfachen Zuckern oder acylierten Derivaten der einfachen Zukker substituiert ist, und

   die Hydroxylgruppen der einfachen Zucker oder der acylierten einfachen Zucker mit Toluoyl-, Benzoyl-, p-Chlorbenzoyl- oder Arylalkylgruppen geschützt sind.

Revendications

1. Glycosides de composés stéroïdes de type aglycone, dans lesquels :

   la position 21 desdits composés stéroïdes est substituée par des sucres simples ou des dérivés acylés desdits sucres simples,
   les groupes hydroxyle desdits sucres simples ou desdits sucres simples acylés sont protégés par des groupes toluoyle, benzoyle, p-chlorobenzoyle ou arylalkyle, et
   lesdits composés stéroïdes consistent en la dexaméthasone, la bêtaméthasone, le dérivé didésacyle du diflu-prédonate, la diflurasone, la diflucortolone ou le valérate de bêtaméthasone

2. Composés tels que définis dans la revendication 1, pour utilisation comme agent anti-inflammatoire.

3. Glycosides de composés stéroïdes anti-inflammatoires de type aglycone pour utilisation comme agent anti-inflammatoire dans lesquels ;

   la position 21 desdits composés stéroïdes est substituée par des sucres simples ou des dérivés acylés desdits sucres simples, et
   les groupes hydroxyle desdits sucres simples ou desdits sucres simples acylés sont protégés par des groupes toluoyle, benzoyle, p-chlorobenzoyle ou arylalkyle.

Fig. 1

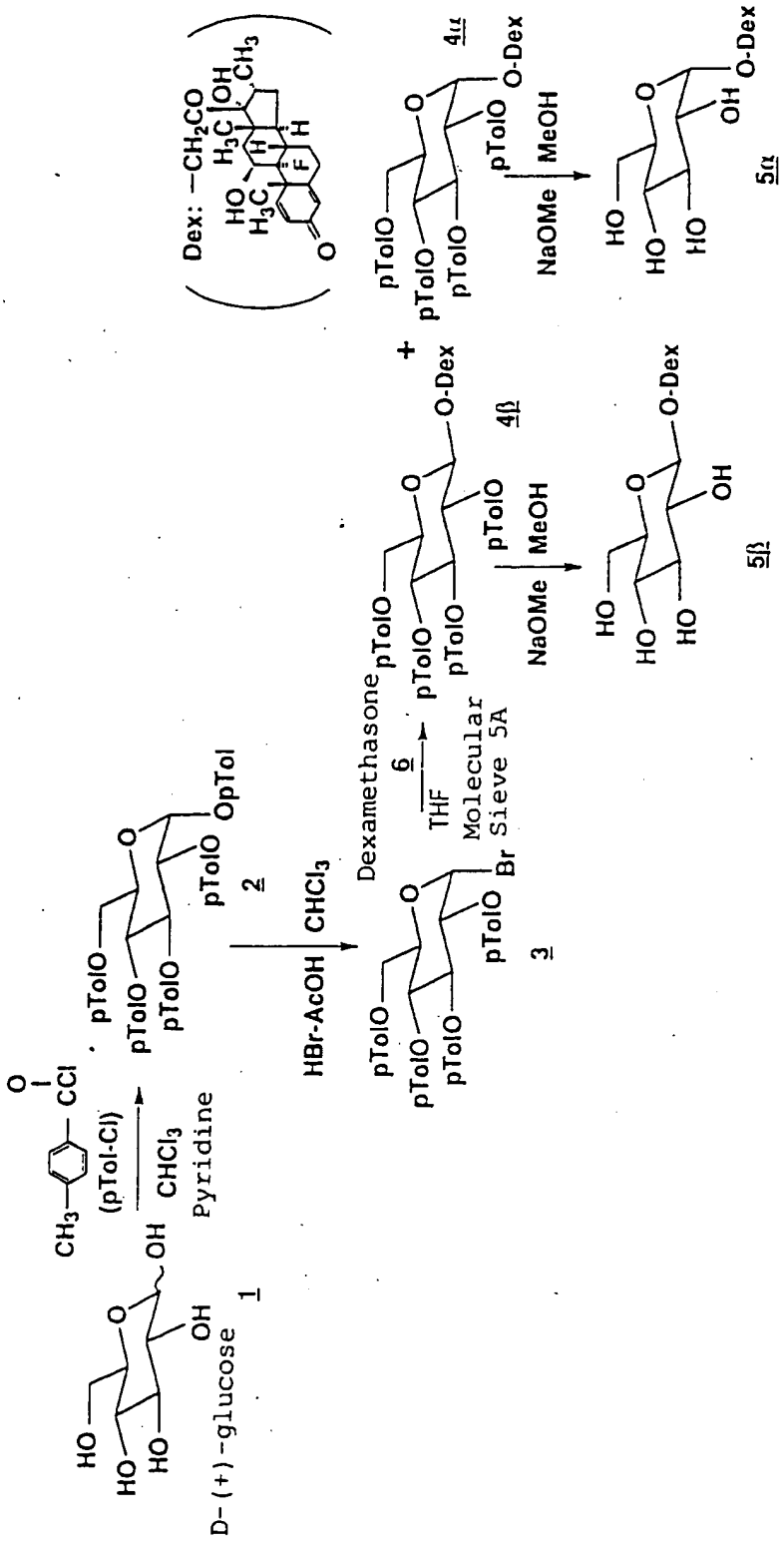
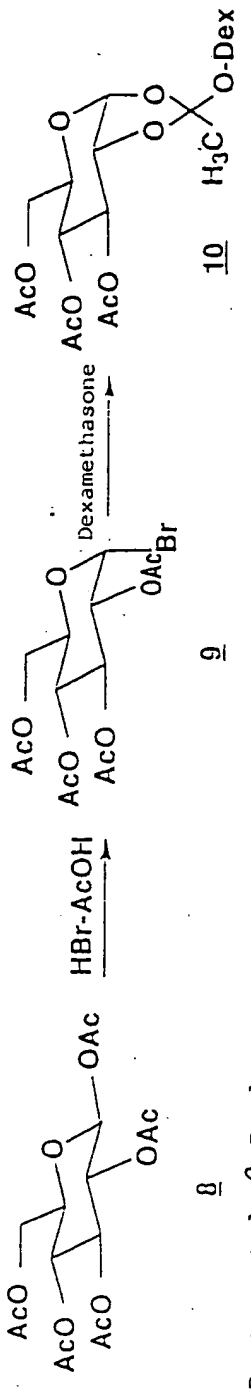

D-(+)-glucose 1
(pTol-Cl)
CHCl3
Pyridine
2
HBr-AcOH
CHCl3
3
Dexamethasone
6
THF
Molecular Sieve 5A
4β
4α
NaOMe
MeOH
5β
5α
Dex: −CH2CO
pTolO
OpTol
Br
O-Dex
HO
OH

Fig. 2



8

9

10

Pentaacetyl-β-D-glucose

Fig. 3

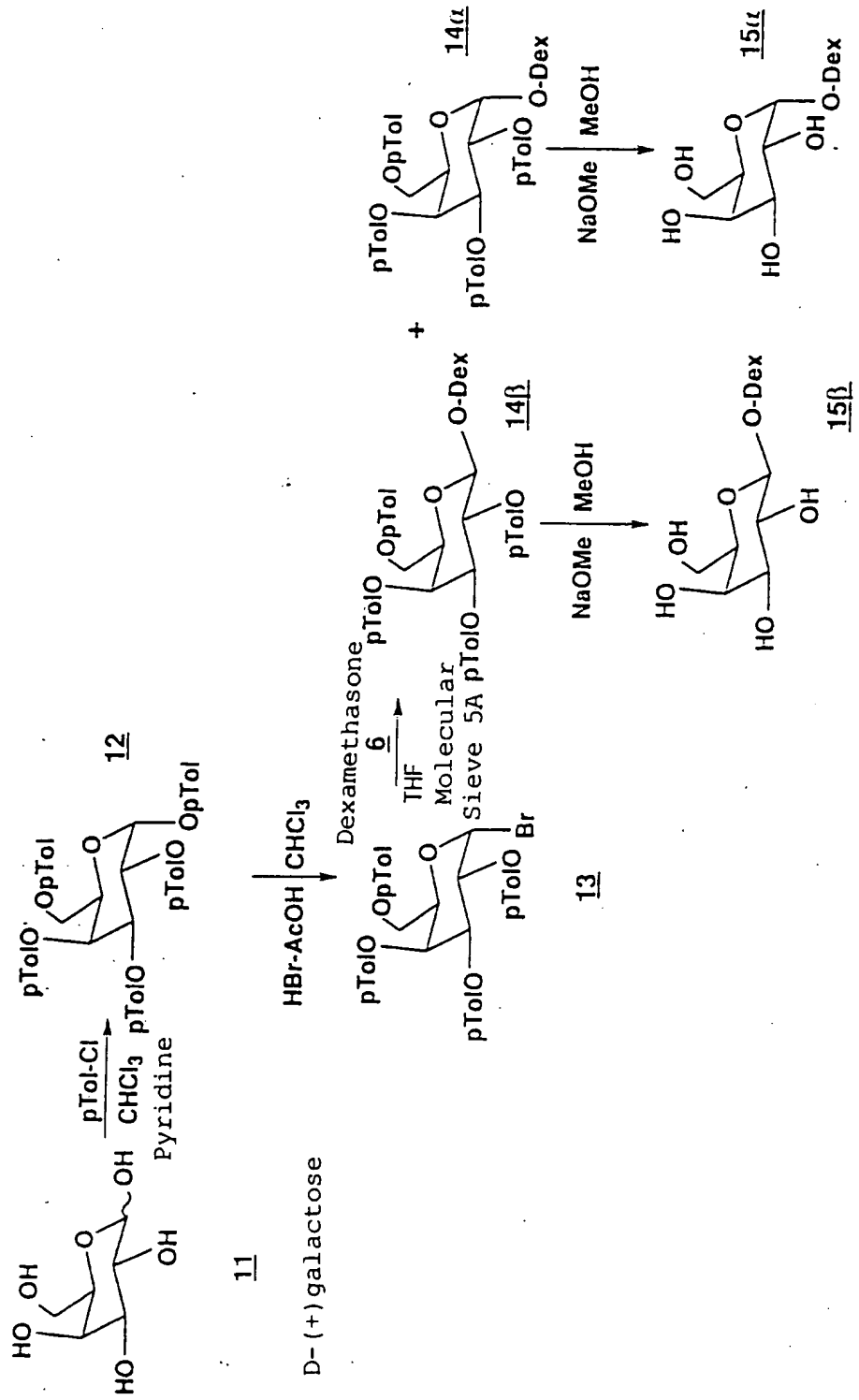

D-(+)galactose
11
pTol-Cl
CHCl3
Pyridine
12
HBr-AcOH
CHCl3
13
Dexamethasone
6
THF
Molecular Sieve 5A
14α
14β
NaOMe
MeOH
15α
15β
pTolO
OpTol
O-Dex
Br
HO
OH

Fig. 4

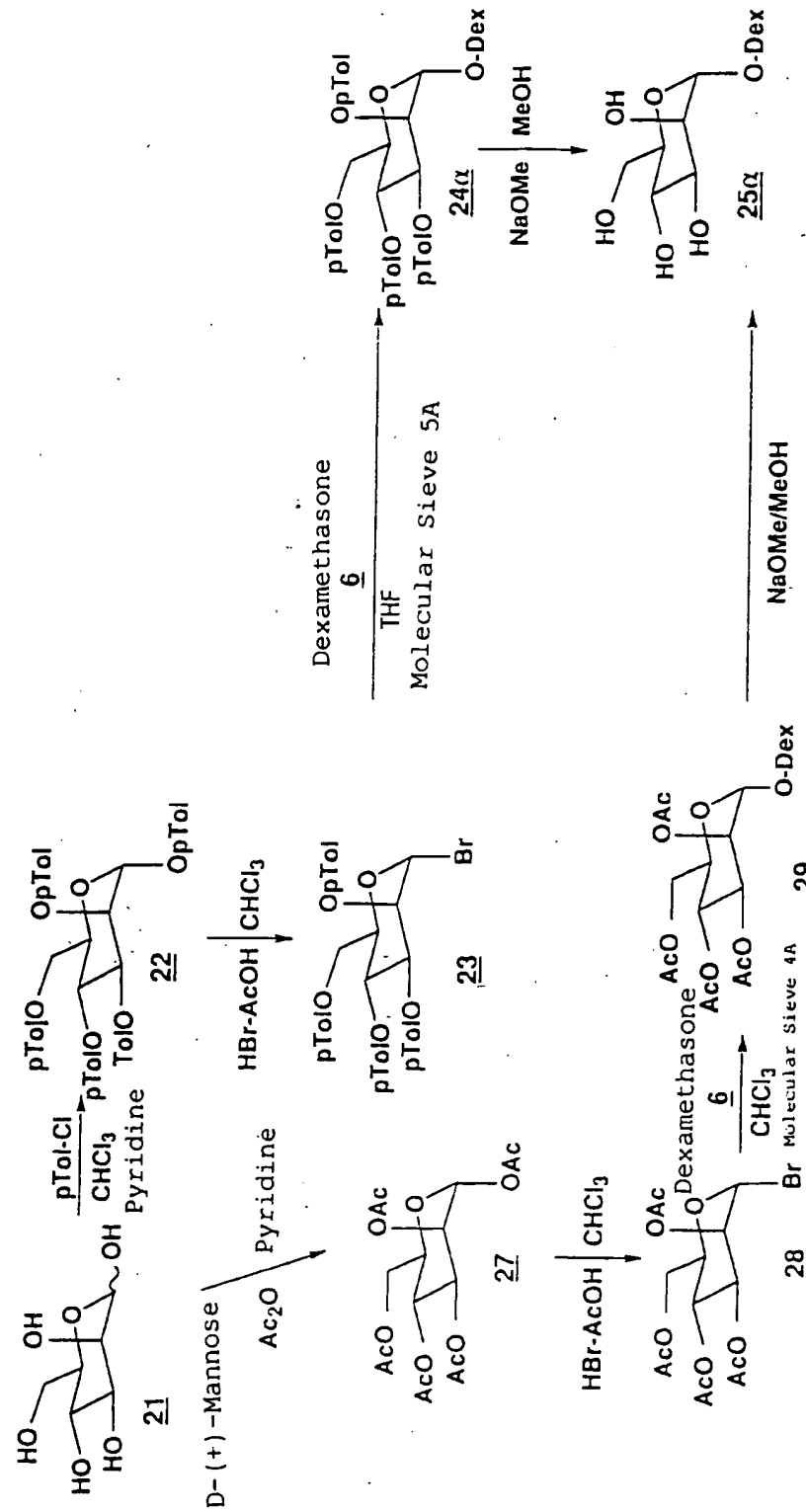

D-(+)-Mannose
Ac2O
Pyridine
21
pTol-Cl
CHCl3
Pyridine
22
HBr-AcOH
CHCl3
23
Pyridine
27
HBr-AcOH
CHCl3
28
Dexamethasone
6
CHCl3
Molecular Sieve 4A
Ag2CO3
29
Dexamethasone
6
THF
Molecular Sieve 5A
24α
NaOMe
MeOH
25α
NaOMe/MeOH

Fig. 5

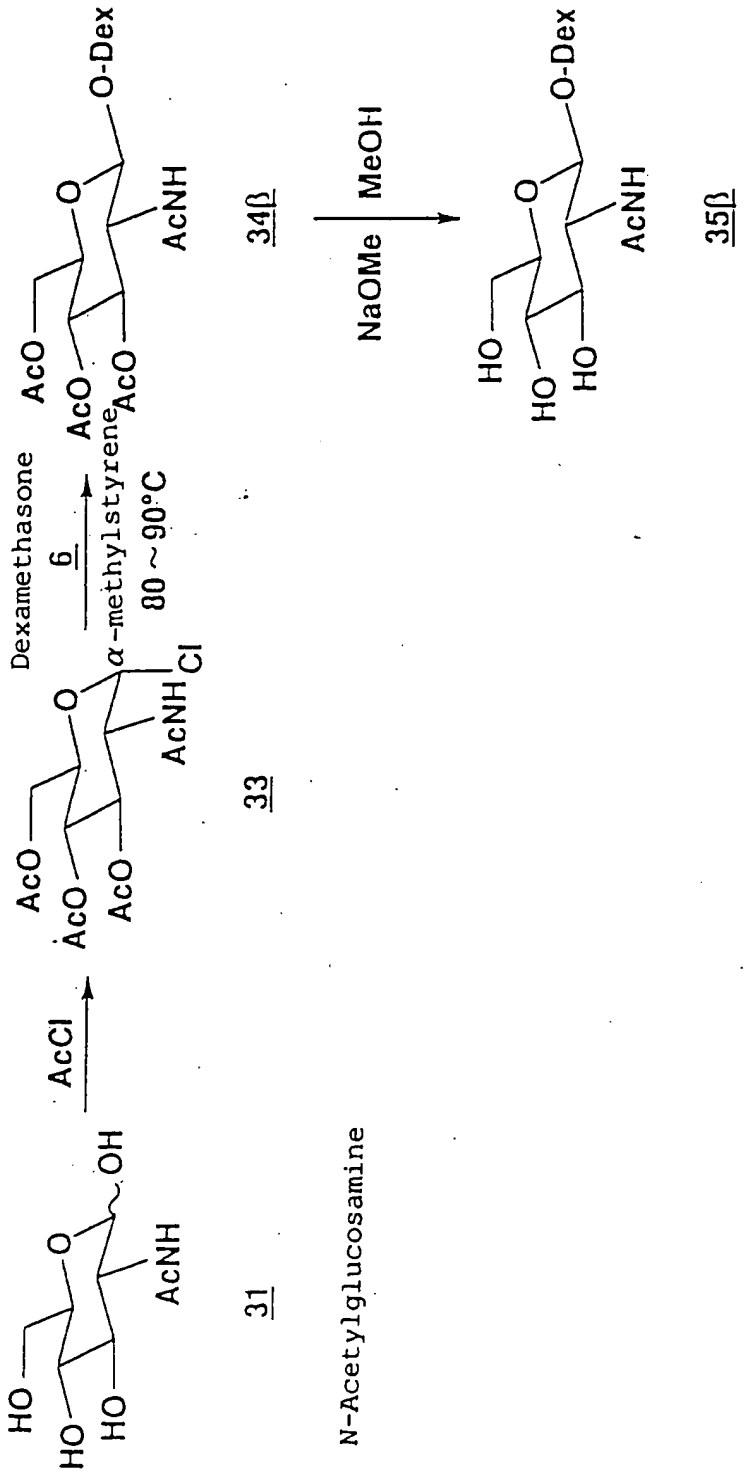

N-Acetylglucosamine
31
AcCl
33
Dexamethasone
6
α-methylstyrene
80 ~ 90°C
34β
NaOMe
MeOH
35β
HO
HO
HO
OH
AcNH
AcO
AcO
AcO
Cl
O-Dex
O

Fig. 6

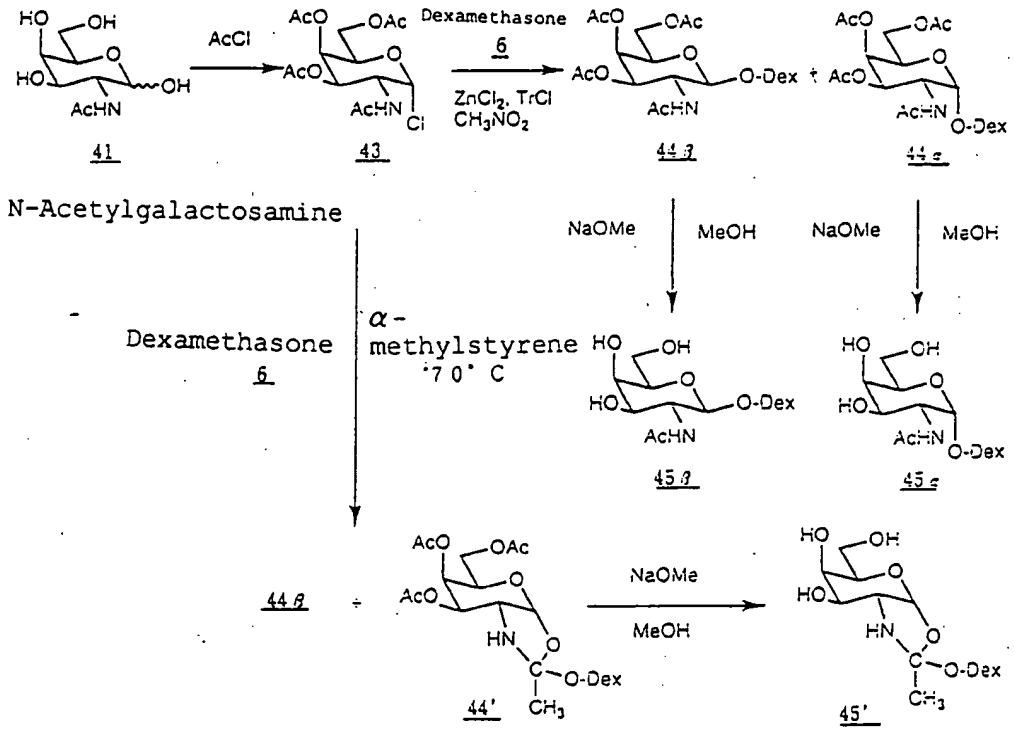

AcCl
Dexamethasone
6
ZnCl2, TrCl
CH3NO2
41
43
44β
44α
N-Acetylgalactosamine
Dexamethasone
6
α-
methylstyrene
70° C
NaOMe
MeOH
NaOMe
MeOH
45β
45α
44β
NaOMe
MeOH
44'
45'

Fig. 7

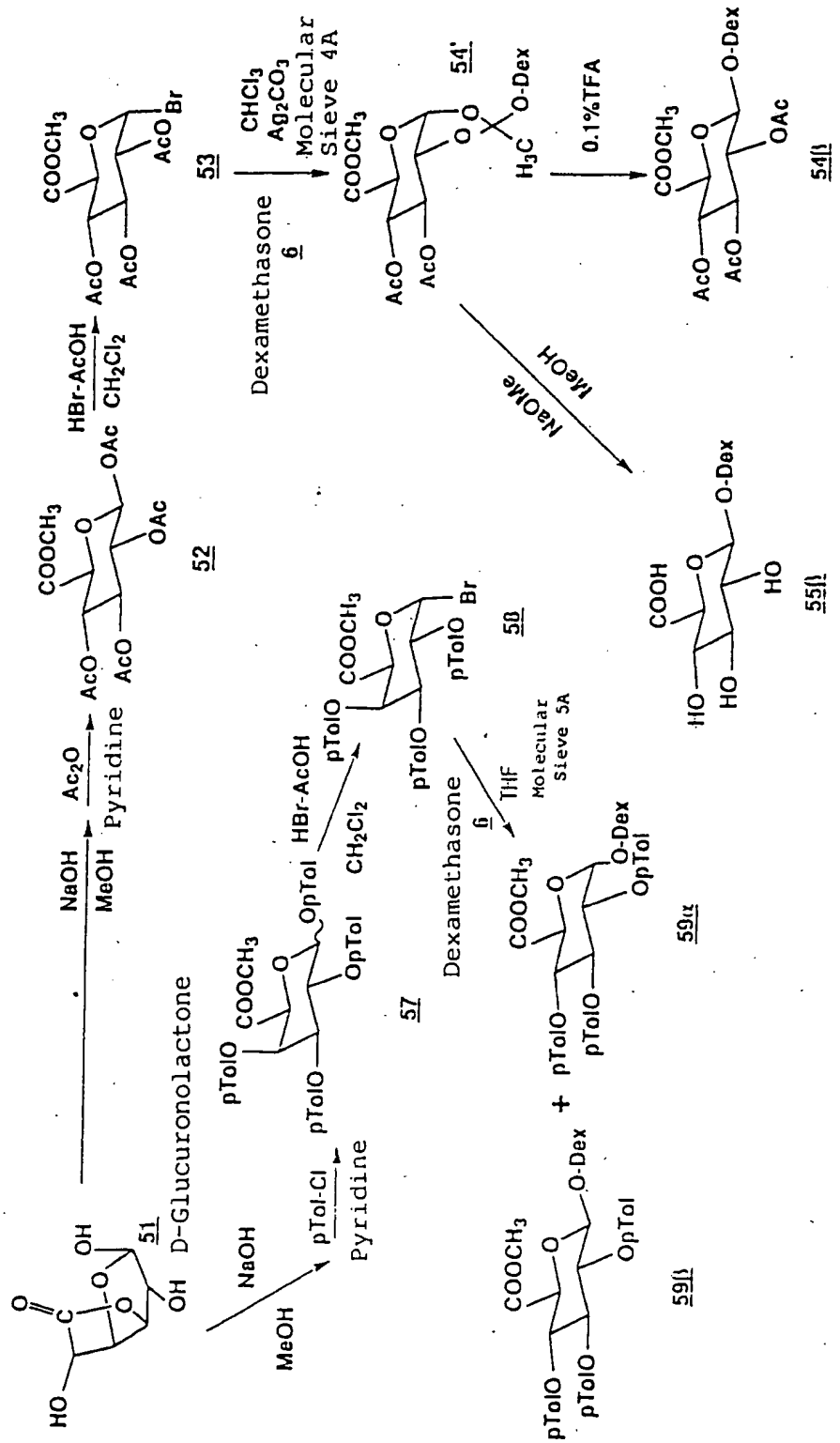

D-Glucuronolactone
51
NaOH
MeOH
Ac2O
Pyridine
52
HBr-AcOH
CH2Cl2
53
CHCl3
Ag2CO3
Molecular Sieve 4A
Dexamethasone
6
54'
0.1%TFA
54β
NaOMe
MeOH
55β
pTol-Cl
Pyridine
57
HBr-AcOH
CH2Cl2
58
Dexamethasone
6
THF
Molecular Sieve 5A
59α
59β

Fig. 8

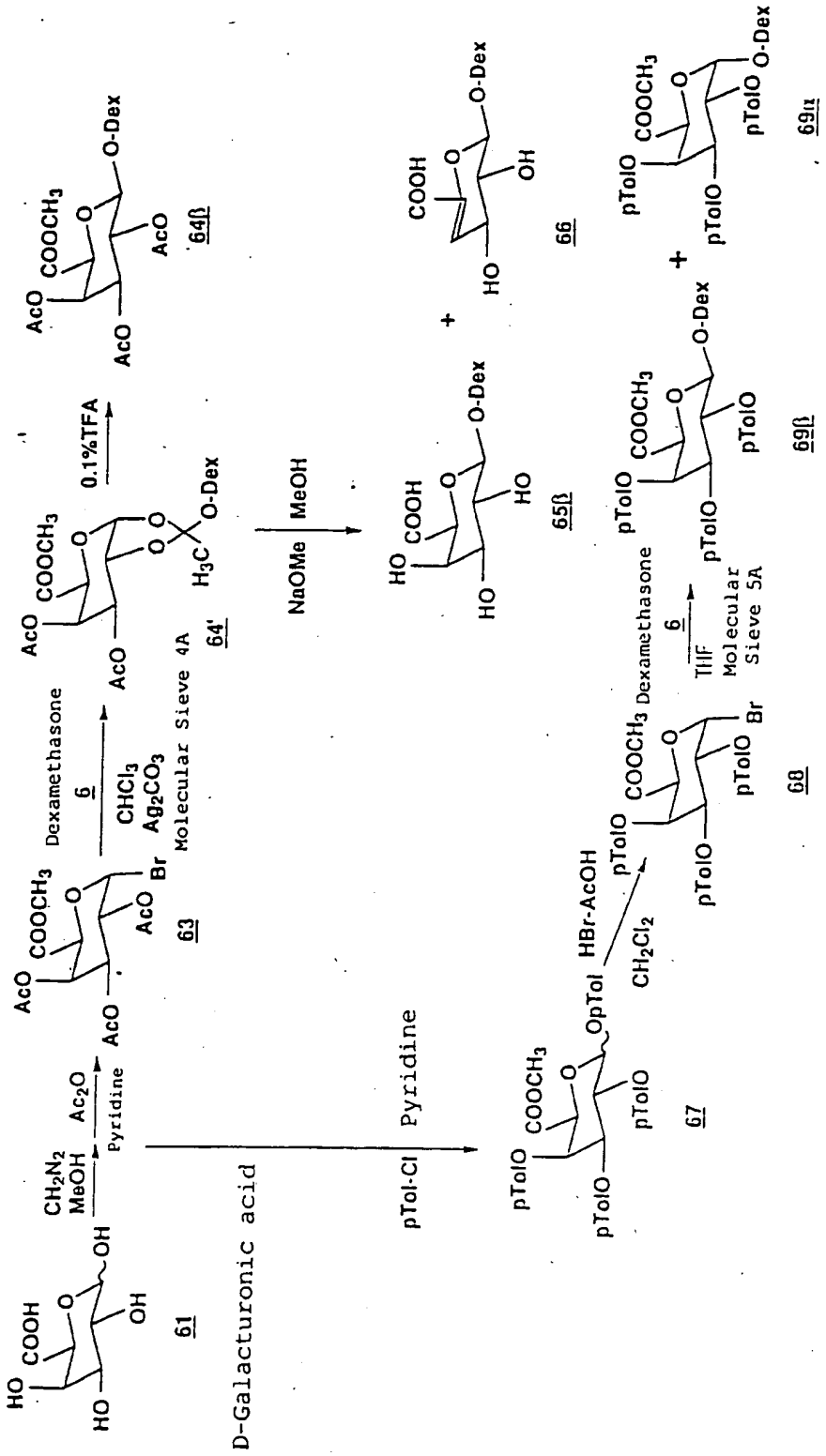

D-Galacturonic acid
CH2N2
MeOH
Ac2O
Pyridine
61
63
Dexamethasone
6
CHCl3
Ag2CO3
Molecular Sieve 4A
64'
0.1%TFA
64β
NaOMe
MeOH
65β
66
pTol-Cl
Pyridine
67
HBr-AcOH
CH2Cl2
68
Dexamethasone
6
THF
Molecular Sieve 5A
69β
69α

Fig. 9

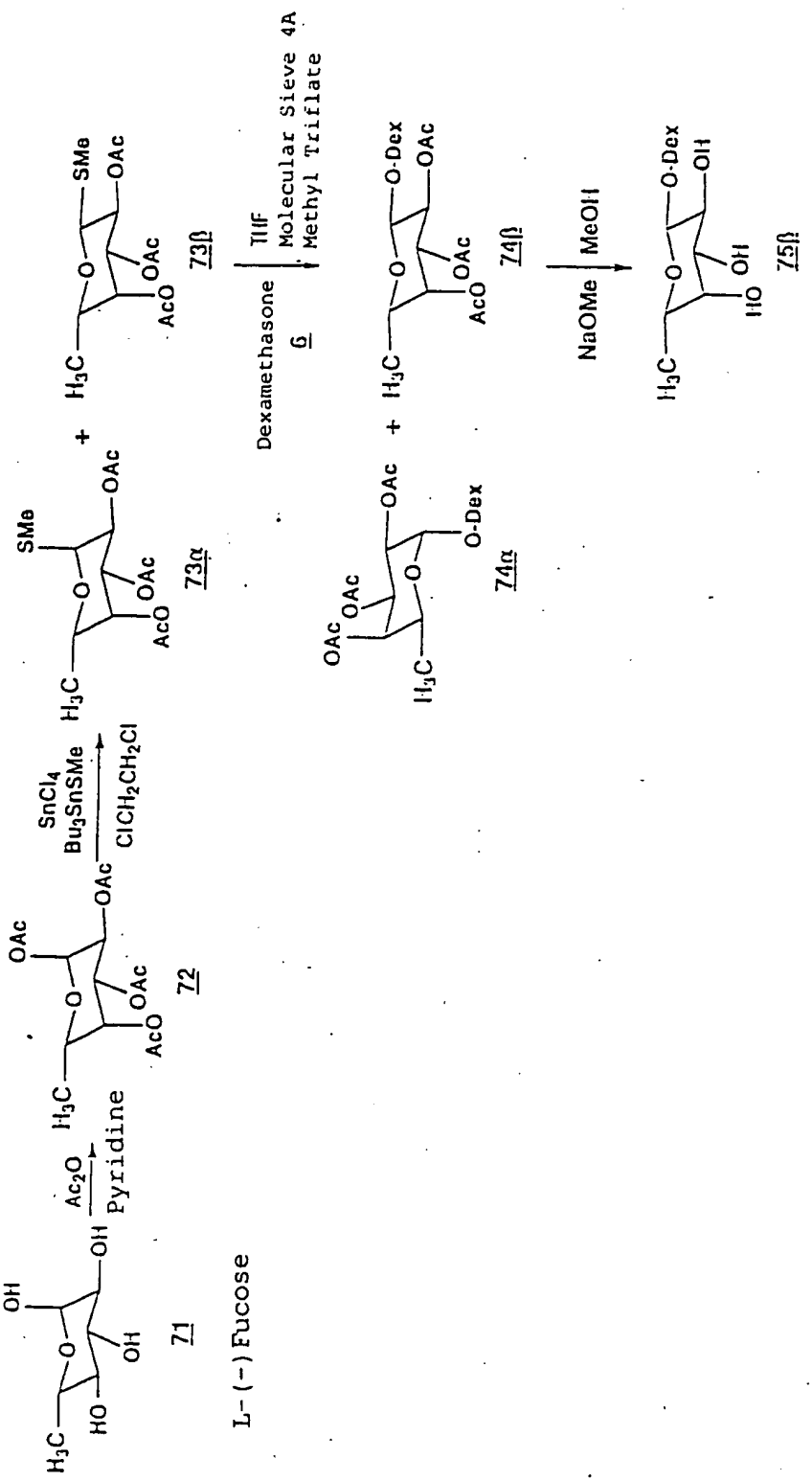

L-(-) Fucose
71
Ac2O
Pyridine
72
SnCl4
Bu3SnSMe
ClCH2CH2Cl
73α
+
73β
Dexamethasone
6
THF
Molecular Sieve 4A
Methyl Triflate
74α
+
74β
NaOMe
MeOH
75β

Fig.10

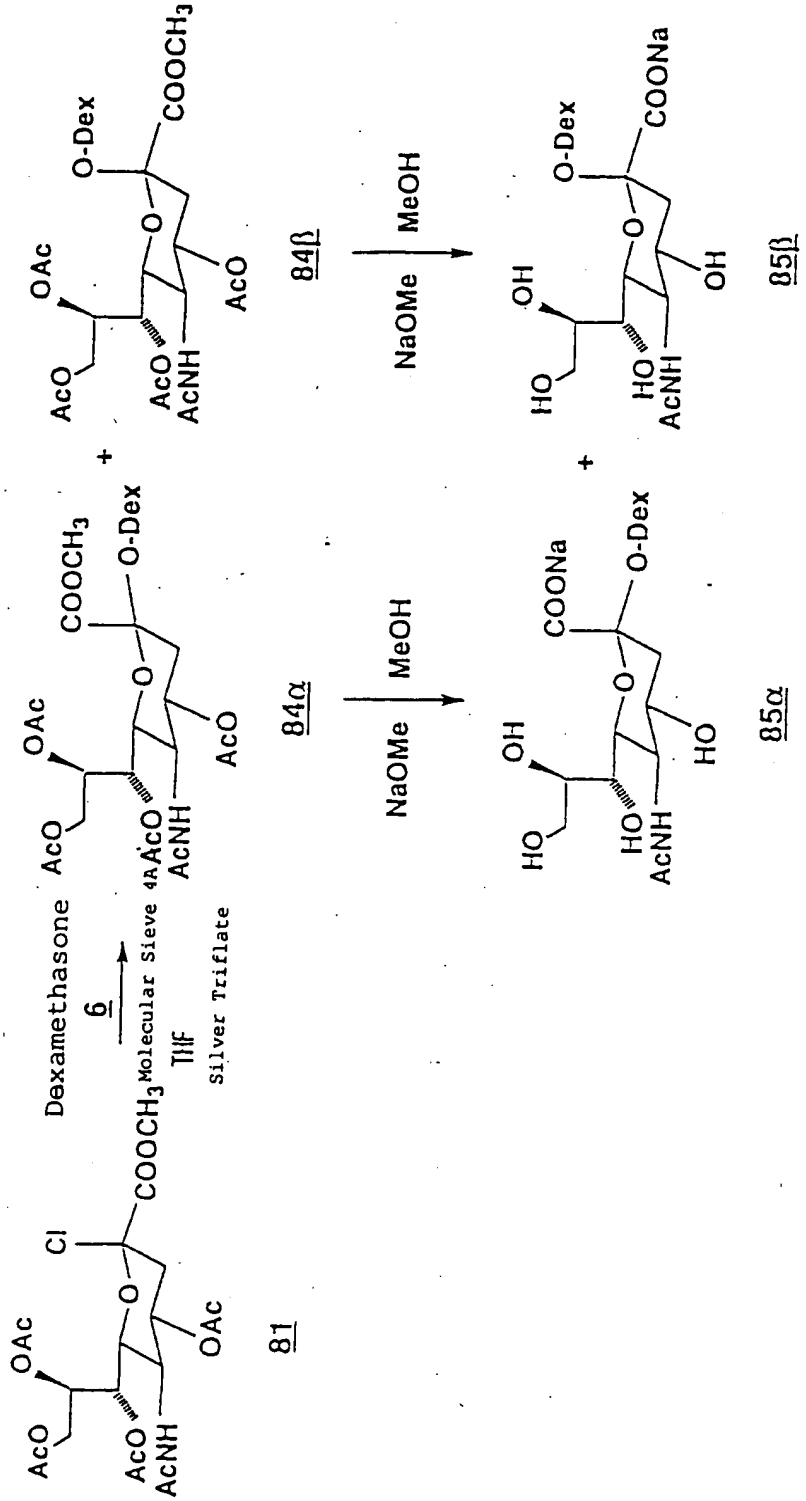

Dexamethasone
6
Molecular Sieve 4A
THF
Silver Triflate
81
84α
84β
NaOMe
MeOH
85α
85β

Fig. 1 1

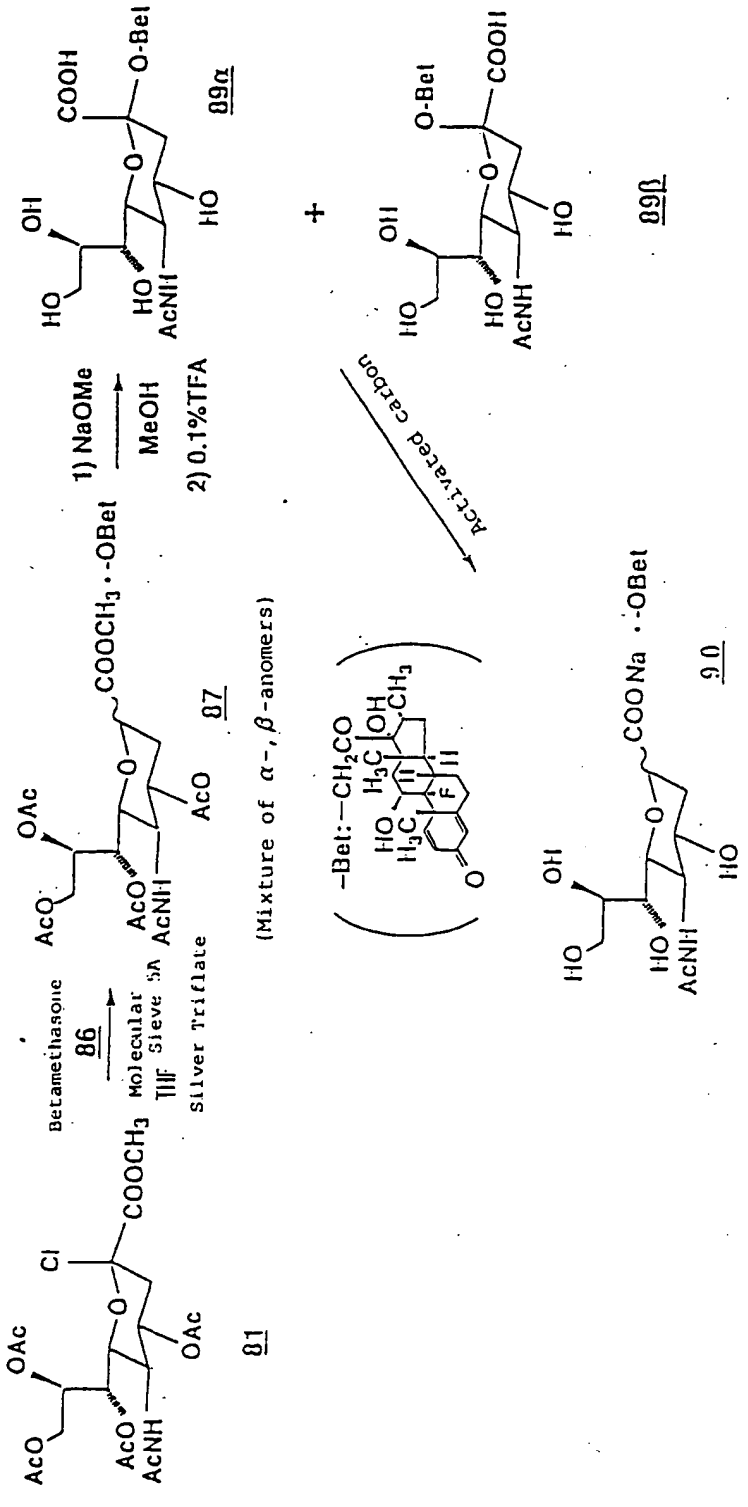
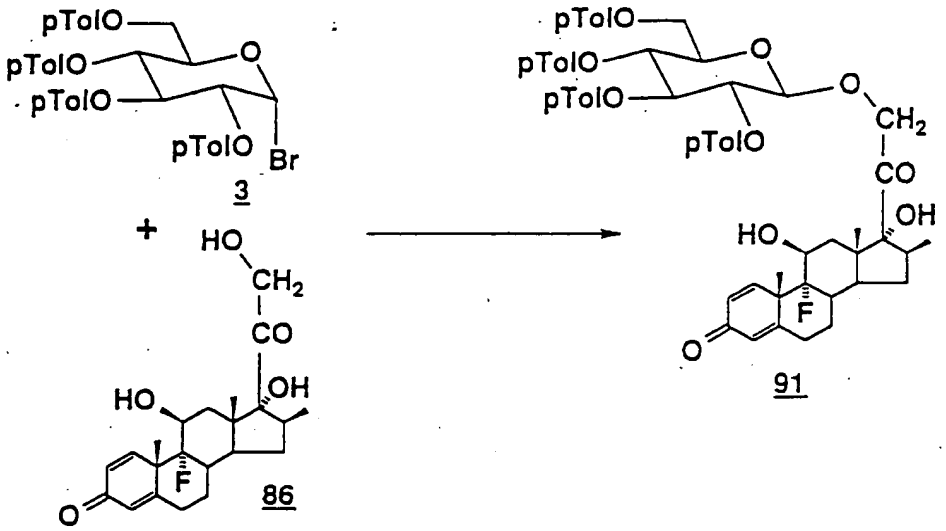

Betamethasone
86
Molecular Sieve 5A
THF
Silver Triflate
91
97
(Mixture of α-, β-anomers)
1) NaOMe
MeOH
2) 0.1%TFA
89α
89β
Activated carbon
90
-Bet: -CH2CO
COOCH3
COOH
COONa
O-Bet
OAc
AcO
AcNH
HO
OH

Fig. 1 2


pTolO
pTolO
pTolO
pTolO
Br
3
+
HO
CH2
CO
OH
HO
F
O
86
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O
O
CH2
CO
OH
HO
F
O
91

Fig. 1 3

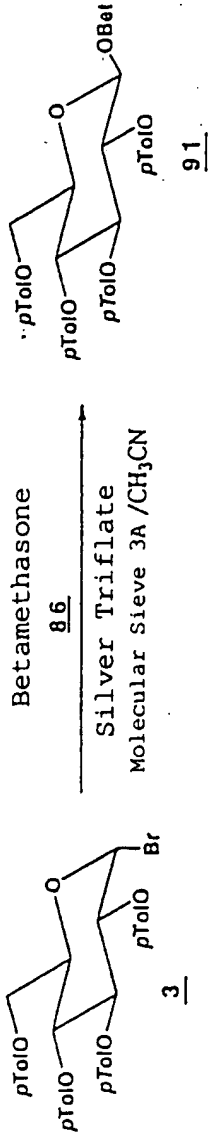

Betamethasone
8 6
Silver Triflate
Molecular Sieve 3A /CH3CN
pTolO
pTolO
pTolO
pTolO
O
Br
3
pTolO
pTolO
pTolO
pTolO
O
OBet
9 1

Fig. 1 4

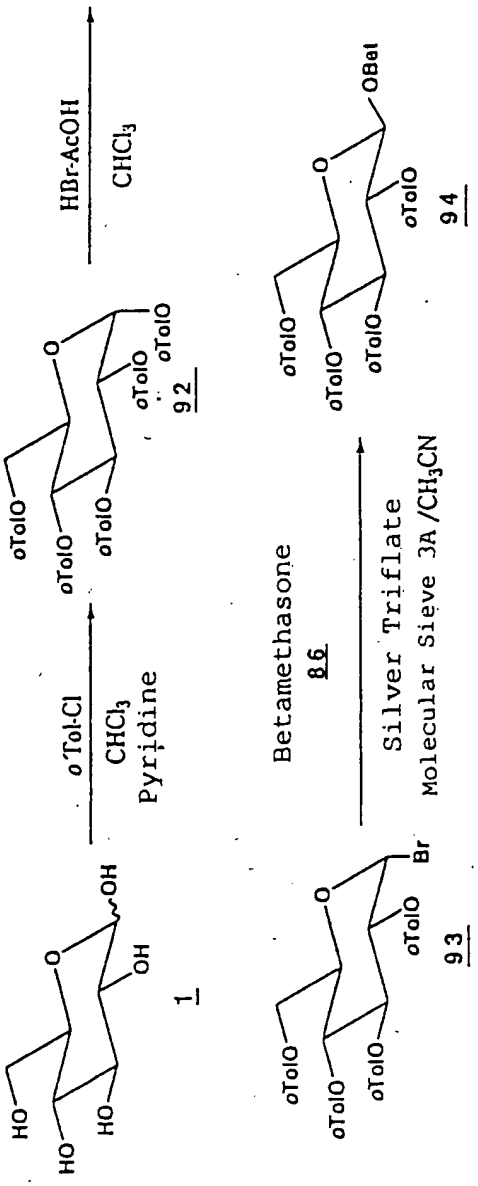

HBr-AcOH
CHCl3
o'Tol-Cl
CHCl3
Pyridine
Betamethasone
86
Silver Triflate
Molecular Sieve 3A/CH3CN
OBal
oTolO
Br
OH
HO
O
1
92
93
94

Fig. 1 5

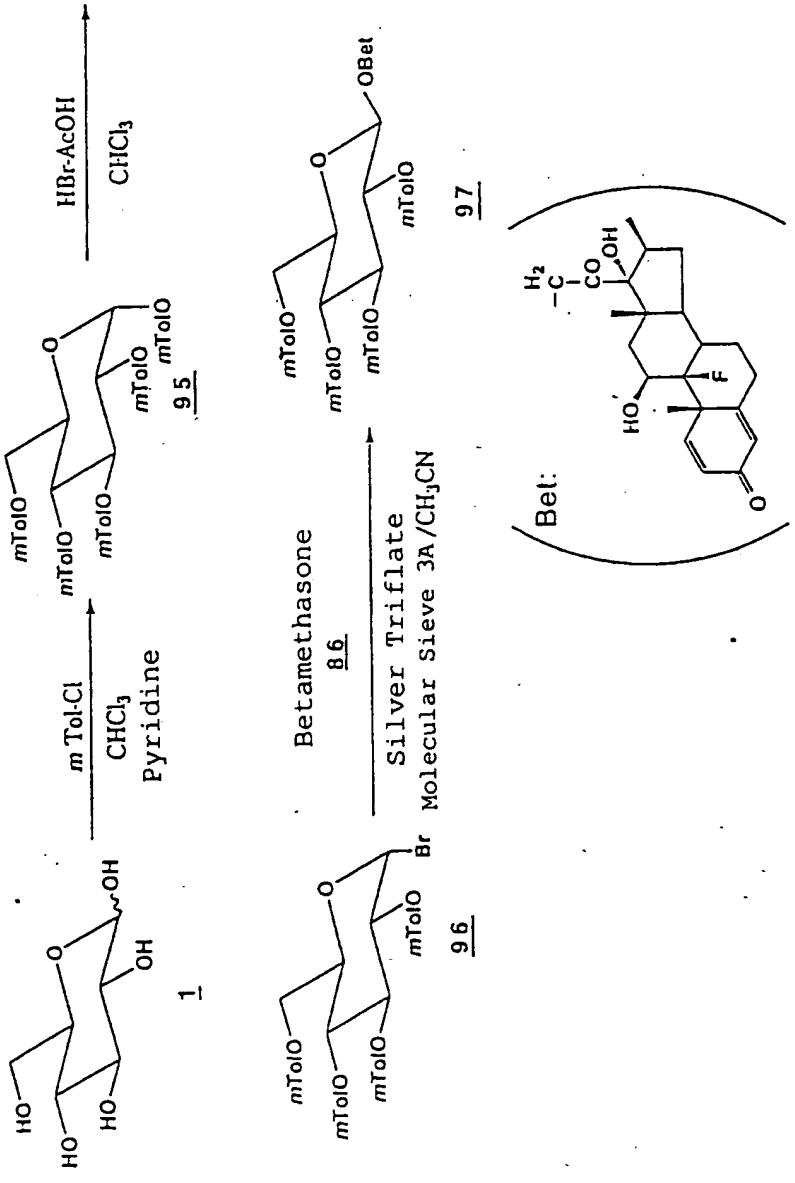

HBr-AcOH
CHCl3
m Tol-Cl
CHCl3
Pyridine
Betamethasone
86
Silver Triflate
Molecular Sieve 3A/CH3CN
mTolO
OBet
OH
HO
Br
Bet:
95
96
97
1

Fig. 16

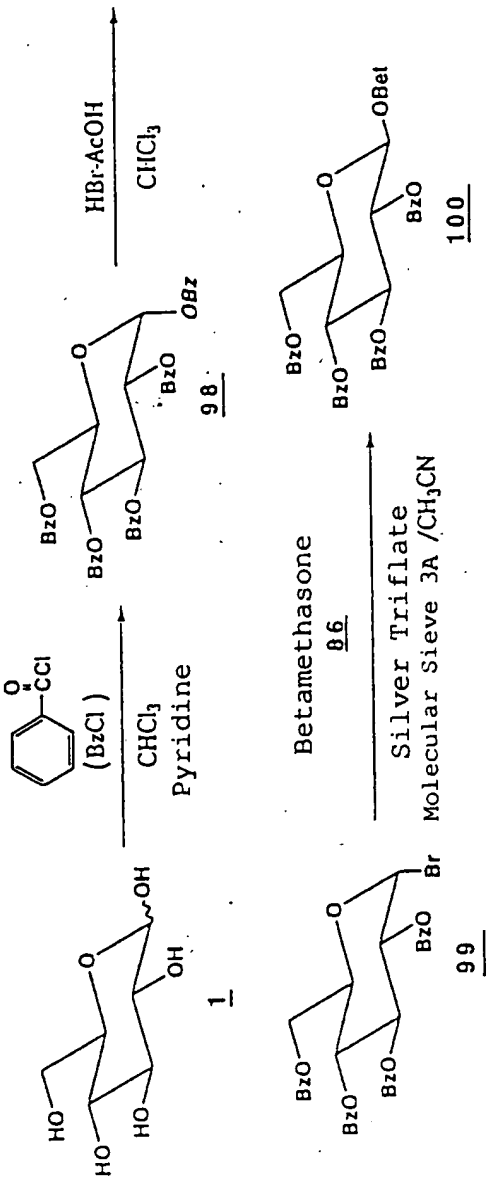

(BzCl)
CHCl3
Pyridine
HBr-AcOH
CHCl3
Betamethasone
96
Silver Triflate
Molecular Sieve 3A /CH3CN
1
98
99
100
OBz
OBet
Br
BzO
HO
OH

Fig. 1 7

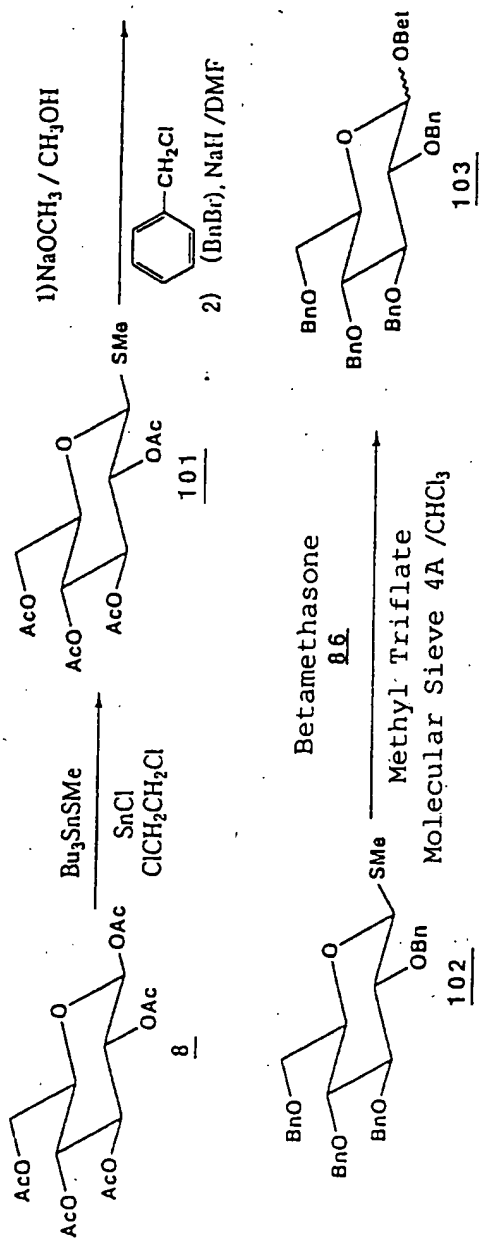

1)NaOCH3 / CH3OH
2) (BnBr), NaH /DMF
CH2Cl
Bu3SnSMe
SnCl
ClCH2CH2Cl
Betamethasone
16
Methyl Triflate
Molecular Sieve 4A /CHCl3
SMe
OAc
AcO
BnO
OBn
OBet
8
101
102
103

Fig. 1 3

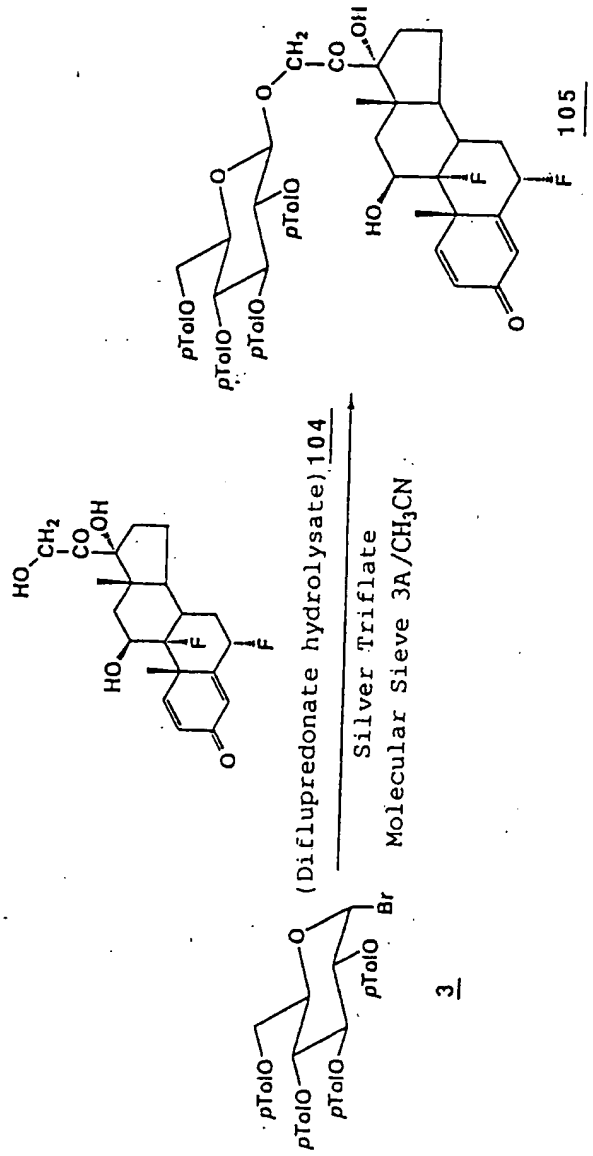

(Difluprednate hydrolysate) 104
Silver Triflate
Molecular Sieve 3A/CH3CN
3
105

Fig. 1 9

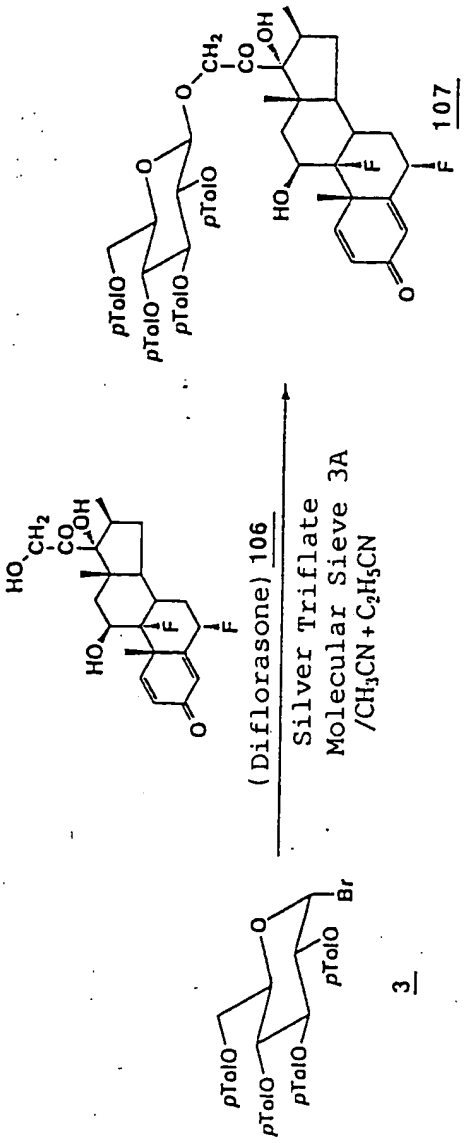

(Diflorasone) 106
Silver Triflate
Molecular Sieve 3A
/CH3CN + C2H5CN
3
107

Fig. 2 0

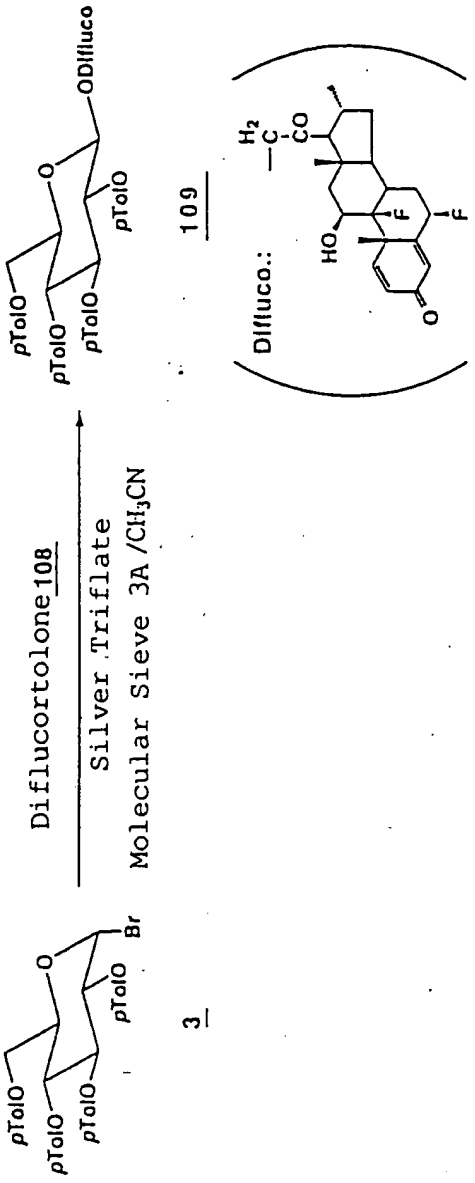

Diflucortolone 108
Silver Triflate
Molecular Sieve 3A /CH3CN
3
109
Difluco.:
pTolO
ODifluco
Br
HO
F
O

Fig. 2 1

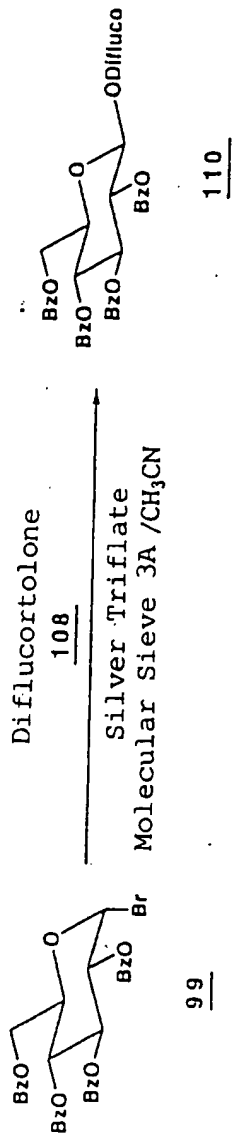

Diflucortolone
108
Silver Triflate
Molecular Sieve 3A /CH3CN
99
110
ODifluco
BzO
Br
O

Fig. 2 2

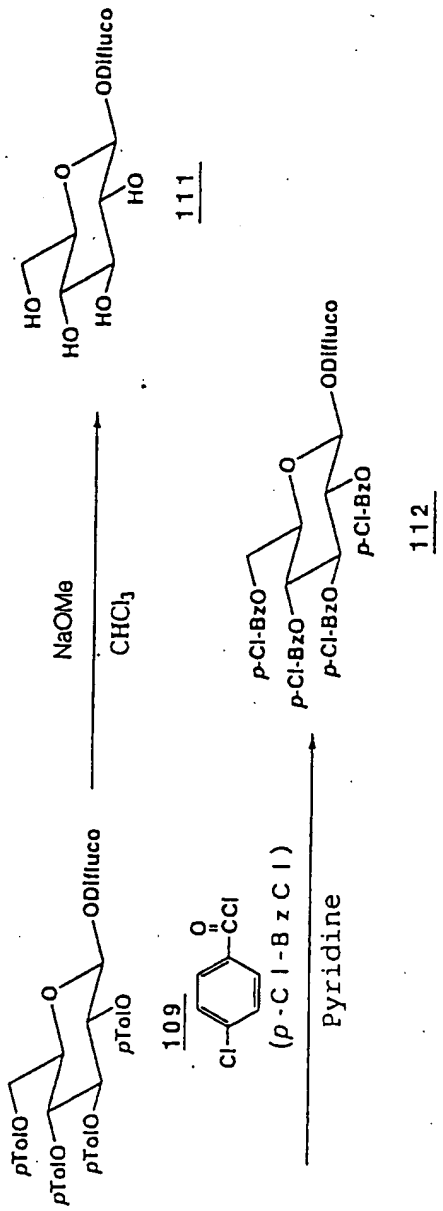

ODifluco
HO
HO
HO
HO
O
111
NaOMe
CHCl3
109
O
CCl
Cl
(p-Cl-BzCl)
Pyridine
p-Cl-BzO
p-Cl-BzO
p-Cl-BzO
112
pTolO
pTolO
pTolO
pTolO

Fig. 2 3

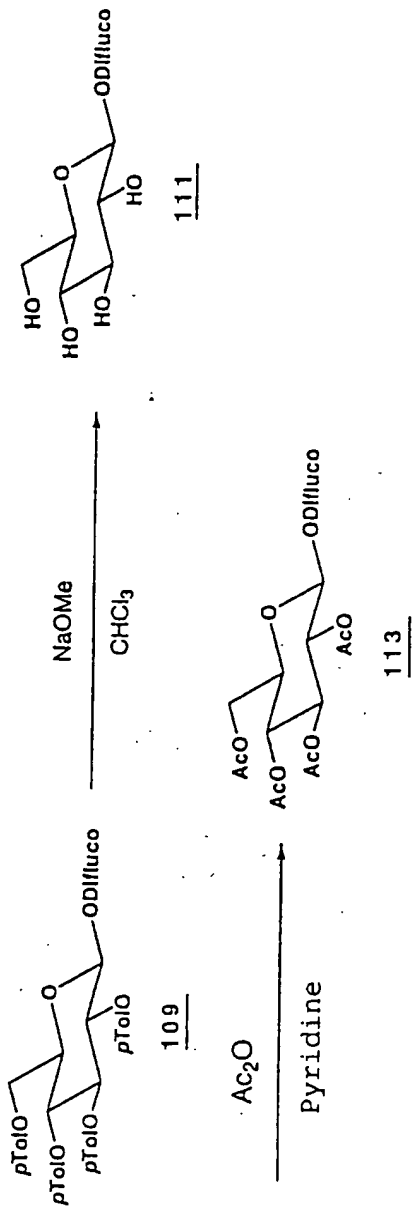

ODIfluco
HO
HO
HO
HO
111
NaOMe
CHCl3
AcO
AcO
AcO
AcO
113
Ac2O
Pyridine
pTolO
pTolO
pTolO
pTolO
109

Fig. 24

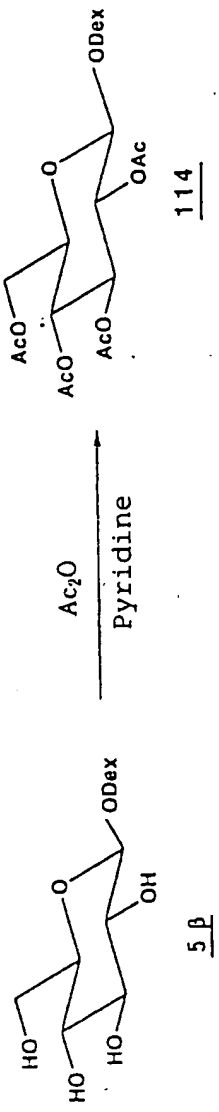
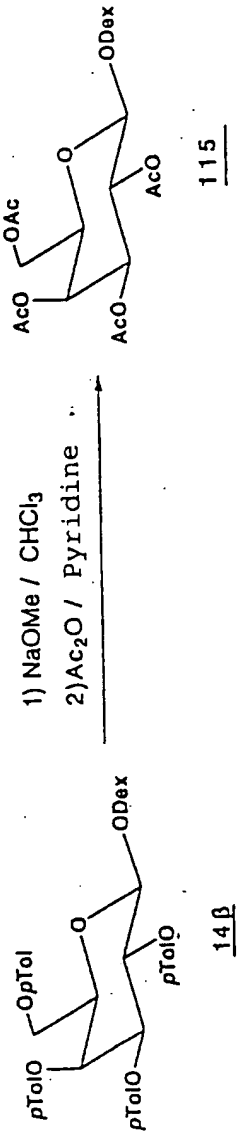


Fig. 25



115

14β

Fig. 2 6

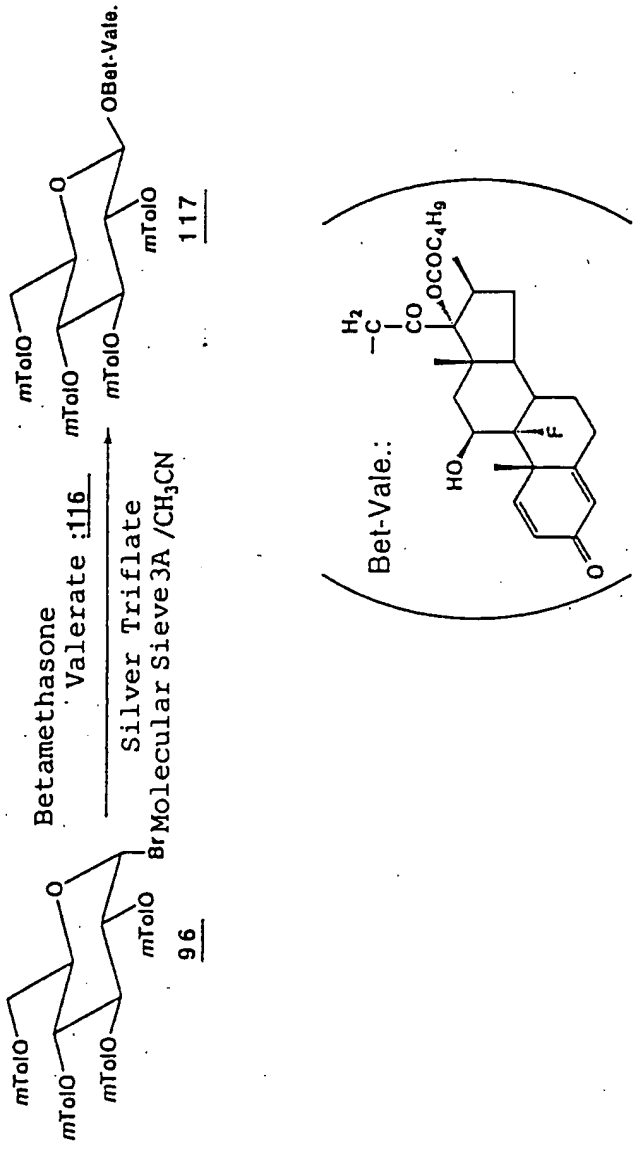
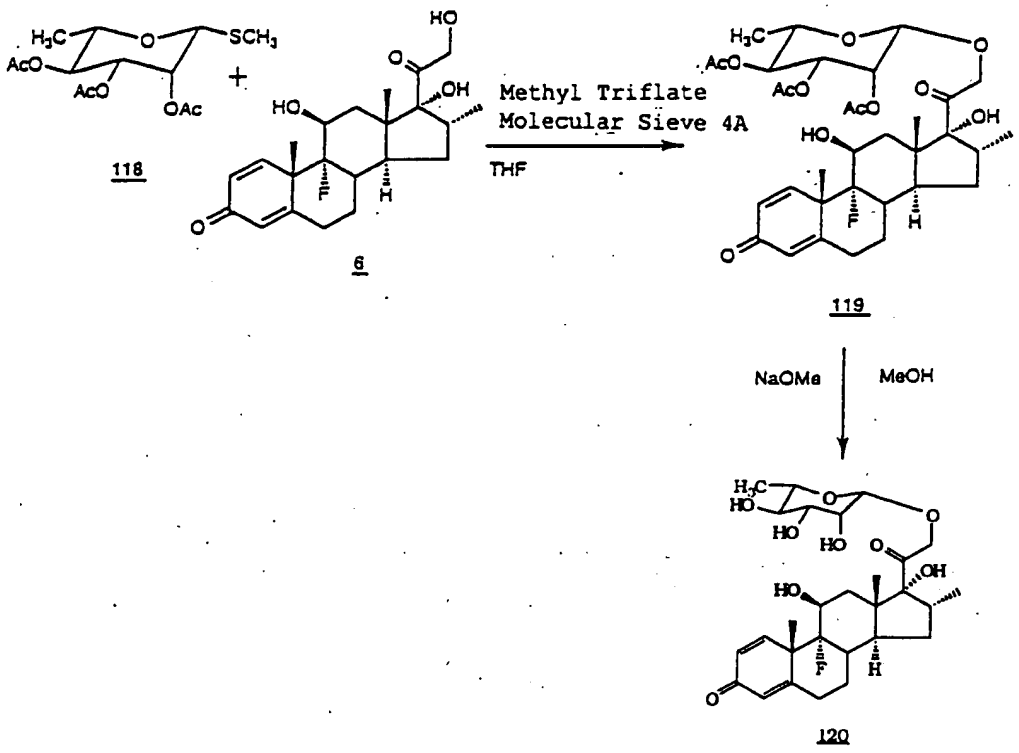

Betamethasone
Valerate :116
Silver Triflate
Molecular Sieve 3A /CH3CN
96
117
mTolO
OBet-Vale.
Bet-Vale.:
H2
C
CO
OCOC4H9
HO
F
O

Fig. 2 7



118

6

119

120